



Occupational Exposure Assessment of Nanomaterials using Control Banding Tools

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Occupational Exposure Assessment of Nanomaterials using Control Banding Tools

Biase Liguori

PhD Thesis
September 2016

DTU Environment
Department of Environmental Engineering
Technical University of Denmark

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The synopsis part of this thesis is available as a pdf-file for download from the DTU research database ORBIT: <http://www.orbit.dtu.dk>

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Preface

This thesis “Occupational Exposure Assessment of Nanomaterials using Control Banding tools” is the result of the PhD study conducted at the Department of Environmental Engineering of the Technical University of Denmark (DTU) from June 2012 to February 2016 under the supervision of Professor Anders Baun and co-supervision of Associate Professor Steffen Foss Hansen and Senior Researcher Keld Alstrup Jensen. The project was partially funded by the ‘Danish Centre for Nanosafety’ and carried out in close collaboration between DTU Environment and the ‘Danish Centre for Nanosafety’ coordinated by the National Research Centre for the Working Environment (NRCWE). One published paper and three journal manuscripts relevant to this thesis were prepared during the course of the study. They are referred to in the text by their roman numerals as Paper **I-IV**.

- I Biase Liguori**, Steffen Foss Hansen, Anders Baun, Keld Alstrup Jensen, 2016a. Control Banding Tools for Occupational Exposure Assessment of Nanomaterials – Ready for Use in a Regulatory Context? *NanoImpact* 2: 1-17
- II Biase Liguori**, Alexander C.Ø. Jensen, Steffen Foss Hansen, Anders Baun, Keld Alstrup Jensen, 2016b. Sensitivity Analysis of the exposure assessment module in NanoSafer version 1.1: Ranking of Determining Parameters and Uncertainty. *Manuscript*
- III** Keld Alstrup Jensen, Anne Thoustrup Saber, Henrik Vejen Kristensen, **Biase Liguori**, Alexander Christian Østerskov Jensen¹, Ismo Kalevi Koponen, Håkan Wallin 2016. NanoSafer version 1.1: A web-based precautionary risk assessment and management tool for manufactured nanomaterials using first order modeling. *Manuscript*
- IV** Marcus Levin; Elena Rojas; Esa Vanhala; Minnamari Vippola; **Biase Liguori**; Kirsten Inga Kling; Ismo Kalevi Koponen; Kristian Michael; Timo Tuomi; Danijela Gregurec; Sergio Moya; Keld Alstrup Jensen, 2015. Influence of relative humidity and physical load during storage on dustiness of inorganic nanomaterials: implications for testing and risk assessment. *Journal of Nanoparticle Research* 17(8):337

In addition, the following publications, not included in this thesis, were also concluded during this PhD study:

Kevin Shahbazi, Biase Liguori, Anders Baun. "A procedure for evaluating potential human and environmental exposure to nanomaterials in commercial products (NanoPEEP) – Submitted

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I would also like to express my gratitude to *Professor Thomas Højlund Christensens* for the opportunity he gave me to start my experience at DTU Environment a few years ago.

Thanks to my colleagues at the Department of Environmental Engineering at the Technical University of Denmark (DTU) and at the National Research Centre for the Working Environment (NRCWE) for the pleasant and inspiring environment (in particular *Aiga Mackevica, Anne Harsting, Lars Michael Skjolding, Lauge Peter Westergaard Clausen, Nanna Isabella Bloch Hartmann, Rune Hjorth, Sara Nørgaard Sørensen, Torben Dolin, Alexander Christian Østerskov Jensen, Asger Wisti Nørgaard, Brian Hansen, Hans Christian Budtz, Ismo Kalevi Koponen, Joonas Koivisto, Kirsten Inga Kling, Marcus Levin, Marina Moser-Johansen, Rambabu Atluri, Yahia Kembouche*). I would like also express my gratitude to both institutes for the opportunity they gave me.

I would like to thank *Philip Thinggaard* for his help for the translation of the summary into Danish and for the English language revision of the text.

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Biase Liguori

Summary

Nanotechnology can be termed as the “new industrial revolution”. A broad range of potential benefits in various applications for the environment and everyday life of humans can be related to the use of nanotechnology. Nanomaterials are used in a large variety of products already in the market, and because of their novel physical and chemical characteristics, the application of nanomaterials is projected to increase further. This will inevitably increase the production of nanomaterials with potential increase of exposure for the workers which are the first in line expected to become exposed to potentially hazardous nanomaterials.

Exposure assessment of nanomaterials is more difficult to define and conduct than that of traditional chemicals. This thesis provides an analysis of the field of occupational exposure assessment and a number of challenges are identified. The analysis showed that there are in general two approaches to assess the exposure of nanomaterials at the workplace: they can be measured or they can be estimated by modelling. It was pointed out that measurements are the standard approach used for the assessment of workplace exposure. However, as highlighted throughout the analysis, the assessment of conventional chemicals is well established with clear definition of which metric to use (generally mass concentration). For nanoparticles the assessment procedures are not defined yet and there is debate on which metric should be used (e.g., mass, surface, size-number distribution).

Similarly to measurements, it was found that models in general can be used successfully and effectively in assessing the exposure to conventional chemicals. Several models are suggested also by the European Chemicals Agency (ECHA) in the technical guidance document R.14 for the assessment of occupational exposure and some of them are under a validation process. However, difficulties arise when the existing models for chemicals are applied to nanoparticles, because of the rapid changes of the nanoparticles in aerosols, which is mainly due to different processes of transformation (agglomeration and aggregation, deposition, chemical reactions, and potential mixing and interaction between the nanomaterial and the background aerosol). Moreover, there are no extensive historical data for comparison and model calibration.

Nevertheless, as it is illustrated throughout this thesis, application of modelling for occupational exposure assessment to nanomaterials is still a promising route.

A few years ago a new conceptual model for the assessment of inhalation exposure to nanomaterials was developed. As illustrated in this thesis, this new model includes considerations on nanoparticles behaviour and physical and chemical properties. In addition, several Control Banding (CB) tools for estimating the exposure to nanomaterials have been developed. An evaluation of current CB tools showed that they are all meant for a qualitative or semi-quantitative exposure assessment of nanomaterials. Two of these tools, NanoSafer and Stoffenmanager Nano, are relatively advanced, and they are good foundations for an advanced exposure assessment. Considering the tiered approach for workplace assessment proposed by the OECD, these two tools could be situated, between Tier 1 (Information gathering) and Tier 2 (Basic exposure assessment).

Moreover, the thesis and the included scientific papers provide an in-depth analysis and a case study of CB tools. A set of parameters were identified which should always be taken into account for occupational assessment of inhalation exposure to nanoparticles. Harmonization considering a set of parameters was encouraged in order to pursue the development of an advanced CB tool for occupational exposure assessment to nanomaterials.

Such as model could be a suitable strategic component for a first exposure assessment and may also improve the risk communication between stakeholders involved in risk assessment of nanomaterials at the workplace.

Sammenfatning (Danish)

Nanoteknologi er blevet kaldt den “nye industrielle revolution” og brugen af nanoteknologi kan medføre en lang række fordele i forskelligartede anvendelser i vores omgivelser og hverdagsliv. Nanomaterialer bruges allerede i mange forskellige produkter på markedet, og på grund af deres nye fysiske og kemiske egenskaber regner man med, at brugen af nanomaterialer vil øges yderligere. Dermed vil det kan produktionen af nanomaterialer øges, og arbejdere vil potentielt kunne blive udsat for nanomaterialer i højere grad, idet de er de første, der forventes at komme i kontakt med nanomaterialerne.

Det er mere vanskeligt at foretage eksponeringsvurderinger af nanomaterialer end af traditionelle kemikalier. Denne afhandling analyserer og diskuterer forskellige metoder til at vurdere arbejdspladseksponeringen og udpeger en række udfordringer forbundet dermed. Overordnet set findes der to metoder til at vurdere eksponering, nemlig enten ved at måle eller ved at et foretage skøn ved hjælp af modeller. I afhandlingen fastslås det, at målinger er standardmetoden for eksponeringsvurderinger på arbejdspladsen. Flere steder i analysen pointeres det, at vurdering af konventionelle kemikalier er veletableret og finder sted efter en klar definition af, hvilken målemetode og måleenhed, der er de bedst egnede (ofte massekoncentration). Med hensyn til vurdering af nanopartikler er fremgangsmåden endnu ikke fastlagt, da der er uenighed om, hvilke typer af målinger og hvilke måleenheder, der bør bruges (fx masse, overflade, fordeling mellem størrelse og antal).

Undersøgelserne i afhandlingen viser, at modeller overordnet set er hensigtsmæssige og effektive til vurdering af eksponering over for konventionelle kemikalier. Det Europæiske Kemikalieagentur (ECHA) foreslår i den tekniske vejlednings kapitel R.14 en række modeller til vurdering af eksponering på arbejdspladsen, og nogle af disse modeller er for tiden ved at blive kalibrerede eller validerede. Ikke desto mindre giver det udfordringer, når eksisterende modeller for kemikalier anvendes til at vurdere eksponeringen for nanopartikler. Det er dels på grund af de hurtige forandringer, som støv med nanopartikler gennemgår, mens de er i luften (agglomerering og aggregering, aflejring, kemiske reaktioner og potentiel blanding og samspil mellem nanomaterialet og det omgivende aerosol). Dertil kommer, at der ikke findes omfattende historiske data, der kan danne grundlag for sammenligning og kalibrering af modeller. Ikke desto mindre, og som det fremgår af denne afhandling, udgør anvendelse af modeller stadig en lovende fremgangsmåde til vurdering af eksponering for nanomaterialer på arbejdspladsen.

Inden for de seneste år er der udviklet en ny begrebsmodel til vurdering af inhalationseksponering over for nanomaterialer. Som det fremgår af afhandlingen omfatter denne nye model betragtninger om forandringer i de luftbårne partiklers fortynding, størrelsesfordeling og koncentration som funktion af betingelserne i arbejdsområdet. Desuden er der udviklet en række CB-værktøjer (Control Banding) til vurdering af eksponering over for nanomaterialer. I afhandlingen foretages en evaluering af de eksisterende CB-værktøjer for nanomaterialer, og den viser, at de alle er anlagt på en kvalitativ eller semikvantitativ vurdering af eksponeringen. To af disse værktøjer, nemlig NanoSafer og Stoffenmanager Nano, er ganske avancerede og danner et solidt grundlag for endnu mere avancerede eksponeringsvurderinger. I lyset af OECD's nyligt publicerede trinvis tilgang til eksponeringsvurderinger på arbejdspladsen, kan disse to CB-værktøjer rubriceres mellem Trin 1 (indsamling af oplysninger) and Trin 2 (grundlæggende eksponeringsvurdering).

Desuden indeholder afhandlingen og de tilhørende videnskabelige artikler en dybdegående analyse og en case-undersøgelse af CB-værktøjer. En række afgørende parametre, som altid bør tages i betragtning ved vurderinger af arbejdspladseksponering over for nanomaterialer ved inhalering, blev herved udpeget. Harmonisering af et sæt af parametre anbefales med henblik på at videreføre udviklingen af avancerede CB-værktøjer til vurderinger af eksponering over for nanomaterialer på arbejdspladsen.

CB-værktøjer kan udgøre en vigtig del af de indledende eksponeringsvurderinger for nanomaterialer på arbejdspladsen og vil kunne bidrage til en forbedret risikokommunikation mellem de interessenter, som er involveret i risikovurdering af nanomaterialer på arbejdspladsen

Alla memoria di mio padre

Antonio Liguori

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1 Background and aim

An estimated 2 million workers around the world die every year from occupational accidents and work-related diseases; in addition ca. 160 million cases of non-fatal work-related injuries and illnesses occur annually (ILO, 2013). Moreover, according to the World Health Organization (WHO) and the International Labour Organization (ILO) many of the worlds' workers do not have access to occupational safety, health and hygiene experts (OSHH) to address and reduce occupational risks they are exposed to (ILO 2003, 2014).

The risks that workers face are well understood in the OSHH scientific literature, however, a simplified strategy for delivering solution to workers facing occupational risk is missing (Zalk DM, 2010). In recent years, a strategy known as Control Banding (CB) has offered a simplified approach for reducing work-related risks. It provides an opportunity to deliver a method to reduce occupational risks for workers who do not have access to an OSHH specialist (Zalk DM, 2010). Conventional risk assessment and management approaches have been challenged in recent years by the rapid growth of nanotechnology. CB can then be an alternative qualitative administrative approach to normal industrial hygiene measurements that defines risks and levels or types of recommended controls (Maynard 2007; Paik et al. 2008; Schulte et al. 2008; Zalk DM, 2010).

The nanotechnology industry has been referred to as the “new industrial revolution” because of the novel material properties of nanomaterials. Nanotechnology applications occur to diverse sectors such as electronics, clean energy, information and communication, chemistry, biotechnology, health, and the construction industry. It is estimated that by 2020, approximately 20% of all goods manufactured worldwide will involve nanotechnology, which will lead to an increased use of nanomaterials (RNCOS, 2015; ILO, 2010; INAIL, 2011; OECD, 2015).

The increasing use of nanomaterials calls for a need to establish better control through occupational exposure limits (OEL). Currently there is, however, lack of OELs for the various nanomaterials and existing OELs for bulk-size materials are expected to not be valid for nanomaterials. This may result in a high risk that workers are unintentionally exposed to nanomaterials at concentrations where hazardous effects may occur (RNCOS, 2015; ILO, 2010; INAIL, 2011; Schulte PA, 2013).

With these challenges in mind, the aim of this thesis is to identify and assess the existing models for precautionary occupational exposure assessment and to assist the further development of CB models.

To address this goal, the aim of the thesis is to:

- Evaluate existing tools and their applicability for industrial and regulatory use with a special focus on the occupational exposure assessment of nanomaterials
- Identify the important parameters needed to support existing tools for assessing potential exposure to nanomaterials in specific work scenarios

“In the thesis an overview of occupational exposure assessment and conceptual modelling approach is provided in Chapter 3; an introduction to CB tools and an identification of the most important key parameters for exposure assessment in Chapter 4; and a sensitivity analysis case study on one of the current CB tools for nanomaterials in Chapter 5. Finally, a set of parameters to be included in exposure models for nanomaterials is suggested in Chapter 6.

However, as fundamental information to the readers, the thesis begins with an introduction to nanotechnology and nanomaterials in Chapter 2 in order to explain why a specific exposure (and risk) assessment is needed for nanomaterials.

2 Nanotechnology and Nanomaterials

Nanotechnology has a vast range of applications and large potential benefits for humans and the environment. The rapid growth of the nanotechnology industry will, however, result in an increasing production of nanomaterials with a consequence of increasing the risk of potential exposure to humans and the environment (Lead and Smith 2009).

Nanotechnology is cross-disciplinary and includes a wide range of techniques, tools and potential applications by controlling shape and size on a nanometre scale (Kosk-Bienko 2009; Lead and Smith 2009). Nanotechnology was conceptually presented for the first time in 1959 when physicist Richard Feynman gave his famous speech, “There is plenty of room at the bottom”, at the annual meeting of the American Physical Society (Richard P. Feynman 1959; Lead and Smith 2009). In his talk, he explored the possibility of controlling and manipulating materials at the scale of individual atoms. However, it was Professor Norio Taniguchi of Tokyo Science University who formulated the first definition of nanotechnology in 1974 as “the processing of, separation, consolidation, and deformation of materials by one atom or one molecule” (The Royal Society 2004; Lead and Smith 2009).

The prefix *nano* is derived from the Greek word for dwarf. A nanometre (nm) is the equivalent to one-billionth of a metre, or 10 to the power of minus 9 meters (10^{-9}m). Figure 1 shows some examples of micro and nano size differences; including a human hair which is approximately 60 μm (60000nm) wide, a red blood cell which is approximately 7 μm (7000nm) wide, and atoms which are below one nanometre in size, while lung alveoli are approximately 400 μm (400000nm). The sizes of nano-particles can be generally comparable to the sizes of viruses, DNA, and proteins, while micro-particles are comparable to cells, organelles, and larger physiological structures (Buzea et al. 2007).

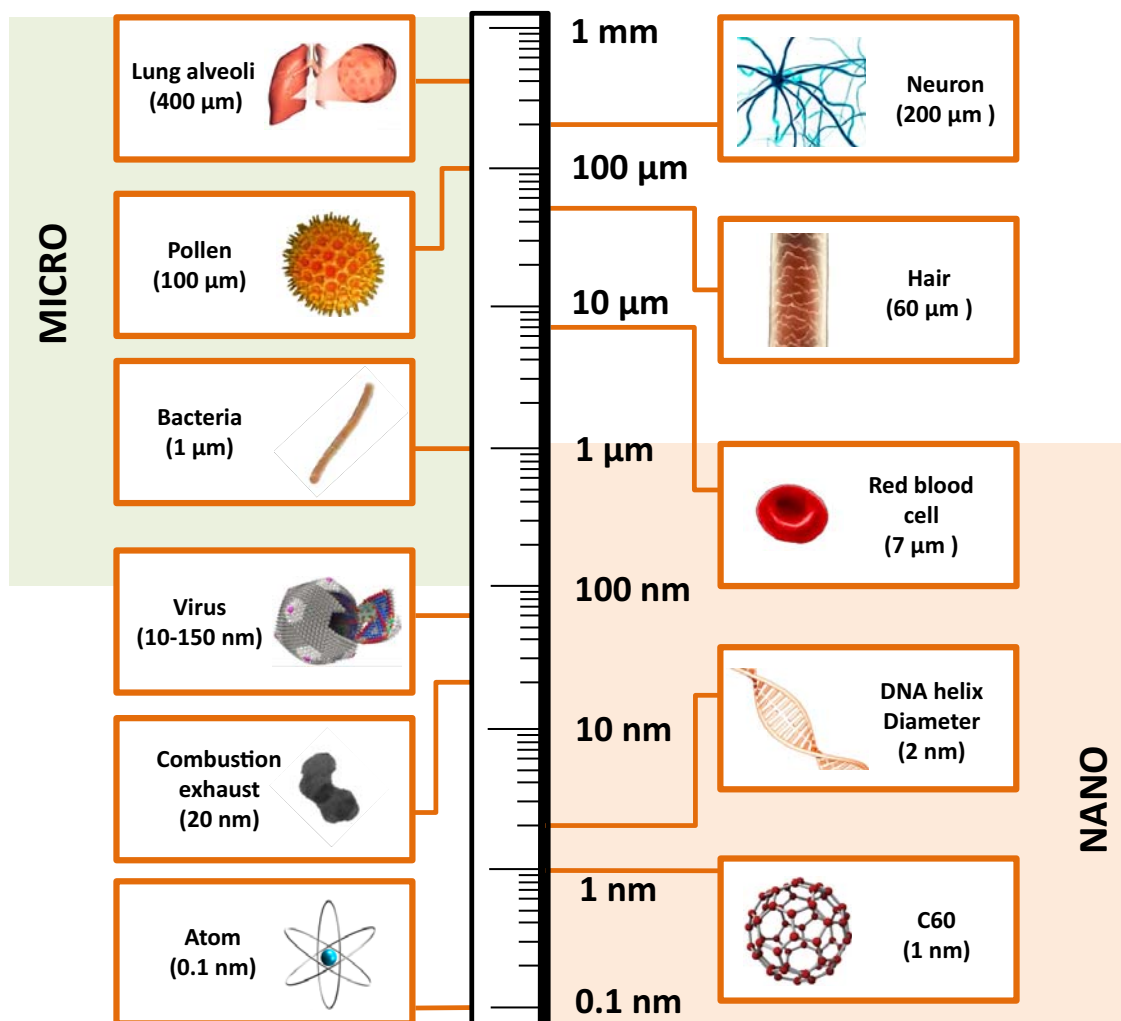


Figure 1 Illustration of the 'nano' and 'micro' sizes of biological components and their comparison with nanomaterials in a logarithmical scale. Adapted from Buzea et al. (2007)

Nanoparticles can occur naturally (i.e. volcanic ash activity, forest fires, sea spray, mineral composites, virus), and they can have human origin: incidental (e.g., cooking smoke, diesel exhaust, welding fumes, industrial effluents) or engineered (e.g., metals, quantum dots, buckyballs/nanotubes, sunscreen pigments) (The Royal Society 2004; Lead and Smith 2009).

Nanomaterials behave significantly different as compared to that of bulk materials and offer various new properties which bring also new risks and uncertainties (Oberdörster 2002; Nel et al. 2006). At the nanoscale, materials can have different or enhanced chemical properties compared with the same materials that are larger. They can be characterized by their chemical reactivity which is also dependent on their larger surface to volume ratio (The Royal Society 2004; ISO 2008a; Lead and Smith 2009). As the size of matter is reduced to the nanoscale, quantum effects can begin to dominate the behaviour,

and these quantum effects can significantly change a material's optical, magnetic or electrical properties (The Royal Society 2004; Lead and Smith 2009). It is therefore important, in an occupational exposure assessment, to discriminate between common materials, bulk materials, and nanomaterials.

Materials engineered to such a small scale are often referred to as engineered or manufactured nanomaterials. In this work, the term nanomaterials (NM) principally refers to the EC recommendation EC 2011 and in particular point 2: "Nanomaterial means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, have one or more external dimensions in the size range 1 nm-100 nm"; and point 5: "In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %". However, when referring to other authors, other terms may have been used therein and can be different to the EC recommendation (EC 2011). The known other terms and definitions adopted by other authors to whom I may refer in this work, are presented below.

The American Society for Testing and Materials (ASTM) International defines nanoparticle as: "a sub-classification of ultrafine particle with lengths in two or three dimensions greater than 0.001 micrometer (1 nanometer) and smaller than about 0.1 micrometer (100 nanometers) and which may or may not exhibit a size-related intensive property. Ultrafine particle, a particle ranging in size from approximately 0.1 micrometer (100 nanometers) to .001 micrometers (1 nanometer)" (ASTM 2012).

The ISO standard definition for a nano-object is termed as: "Material confined in one, two, or three dimensions at the nanoscale with size range from approximately 1 nm to 100 nm. This includes nanoparticles (all three dimensions in the nanoscale), nanofibres (two dimensions in the nanoscale) and nanoplates (one dimension in the nanoscale). Nanofibres are further divided into nanotubes (hollow nanofibre), nanorods (solid nanofibre) and nanowire (electrically conducting or semiconducting nanofibre)" (ISO 2008b).

3 Occupational exposure assessment of chemicals and nanomaterials

This chapter will begin by introducing the occupational exposure assessment of chemicals and introduce a conceptual mechanistic model (Section 3.1). Next, it will outline the REACH – the Registration, Evaluation, Authorisation and Restriction of Chemicals – and the occupational exposure tools for the risk assessment of chemicals as suggested by REACH (Sections 3.2 and 3.3). Then finally, it will briefly introduce the occupational exposure assessment of nanomaterials (Section 3.4).

3.1 Occupational exposure assessment

Human populations may be exposed to substances from several sources and pathways via various exposure routes: inhalation, dermal contact and ingestion; after passage through the environment, as contents in products, and from exposure at the workplace (van Leeuwen and Vermeire 2007; Lead and Smith 2009).

Exposure assessment is an essential part for the risk characterization in the health risk assessment and risk management process. The exposure assessment covers the emissions, pathways and transformation of substances with the aim of estimating the concentration or doses that the environment and humans are/may be exposed to (van Leeuwen and Vermeire 2007).

Human exposure first occurs externally and is defined as the concentration of an agent reaching a receptor. In this work, the term exposure refers to external inhalation exposure.

Humans are continuously exposed to substances (Figure 2). Therefore, it is a broad and complex process to perform a human exposure assessment. Models, which always represent a simplification of this complexity, can be applied to predict the risk. A practical approach is to compartmentalize the exposure assessment to have occupational exposure models for the assessment at workplaces, consumer exposure models for the assessment of consumers, and environmental exposure models for the assessment of the environment (van Leeuwen and Vermeire 2007; Lead and Smith 2009).

Descriptions of work-related diseases can be found already in writings of the ancient Egyptians and Greeks. However, organized workplace risk assess-

ment and management started only in the 20th century (Hutchins B.L. and Harrison A. 1966).

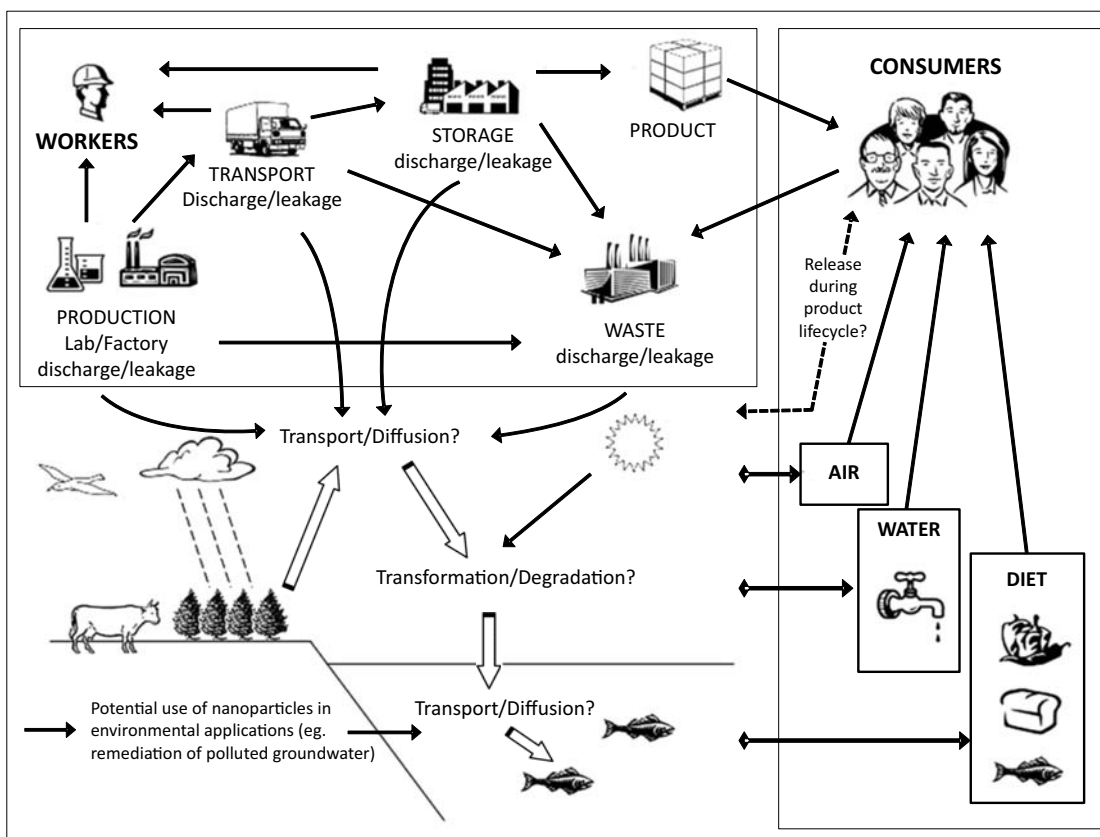


Figure 2 Some possible exposure routes for nanoparticles and nanotubes based on current and potential future applications. Adapted from The Royal Society (2004).

Field measurements and sampling is a standard procedure in the workplace and environment. However, based on all the measurement data, such airborne contaminant concentrations measured with monitoring instruments, statistical models have been developed in order to be able to analyse important parameters of specific tasks or in relation to specific contextual conditions (EC 1994; Kosk-Bienko 2009). Moreover to pre-assess the risks posed by new chemicals or new situations, modelling is the only option, whereas measurement and modelling can be used for the exposure assessment of existing situations (EC 1994; Herber et al. 2001; Schneider 2007; van Leeuwen and Vermeire 2007; Kosk-Bienko 2009). Therefore, mechanistic conceptual models have been developed in order to be able to describe how a substance moves from the source, through the environment and to the receptor (Tielemans et al. 2008; Schneider et al. 2011a; OECD 2015a).

The philosophy behind mechanistic or theoretical approaches is that processes can be quantitatively described based on a theoretical understanding of the

process (van Leeuwen and Vermeire 2007). Figure 3 presents a simplified sketch of a conceptual mechanistic model for inhalation exposure. The graph shows the transport of a contaminant from the source to receptor. The transport from the source into the local control influence region (LCIR) and subsequently in the Near- or Far-Field, including loss of contaminants by deposition on surfaces. In this case, the Near-Field is defined as the volume of air within 1m in any direction of the worker and the Far-Field comprises the remainder of the room (Tielemans et al. 2008).

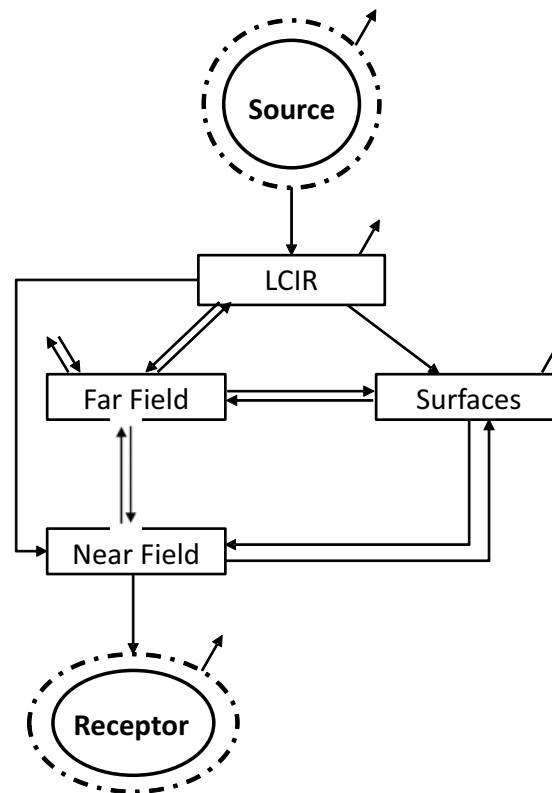


Figure 3 Simplified conceptual mechanistic model for inhalation exposure assessment. The arrows indicate the transport of contaminants between compartments. Dotted lines indicate barriers of exposure control that reduces the amount of contaminants transported between compartments; at source – source enclosure – and at the receptor – personal enclosure. LCIR indicates the local control influence region. Local control systems includes e.g., ventilation or screen or an airborne capture system. Adapted from Tielemans et al. (2008).

It is very important in this model to define all the parameters that determine the connection between the various compartments, from the source to the receptor. Hence, measurement data are fundamental for the calibration of the model.

3.2 Chemicals legislation in the European Union - REACH

A number of conceptual models for exposure assessment have already been used in developing models at various levels within the chemical legislation.

In Europe these models have been used to support the REACH chemicals legislation. REACH is the acronym for the regulatory framework for chemicals i.e. Registration, Evaluation, Authorisation and Restriction of Chemicals – (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 – which came into force on 1 June 2007. It aims to protect human health and the environment from the risks posed by chemicals and promotes an alternative test method. REACH consists of three phases (only a brief summary will be presented in this section, more detail will be given in the following section) in the registration process based on the amount of chemicals that are manufactured, imported or used by companies: The first phase concerned chemicals produced in quantities of more than 1000 tonnes per year; the second phase concerned chemicals produced between 100 and 1000 tonnes per year; and third phase between 1 and 100 tonnes per year. The last phase ends in May 2018 and on this date it will only be possible to commercialize substances registered under REACH (EC 2006).

Moreover, REACH makes the industry responsible for assessing and managing the risks posed by chemicals and responsible for providing appropriate safety information to their users. This has required a lot of work for industry and makes it very difficult or even impossible to operate with the same level of accuracy and precision. Therefore, the European Chemicals Agency (ECHA) has proposed what it has called a tiered approach and has provided a technical guidance document in support of the implementation of the European Chemical legislation, REACH (ECHA 2012b).

The first tier is meant to be a simple screening and allows for a conservative estimate of the exposure. It essentially overestimates the exposure in order to be sure that risk is adequately controlled (van Leeuwen and Vermeire 2007; ECHA 2012b; OECD 2015b). Therefore, if the risk assessment shows that exposure has been controlled sufficiently, no further action is needed. On the other hand, if the assessment shows that there is a risk, it may be necessary to manage the contextual working conditions and repeat the assessment, or it can be decided to do exposure assessment more accurately and go on to a higher tier; by either using a more complex model or by workplace measure-

ments, to find out what the exposure actually is. First tier models are very simple but not very accurate, whereas higher tier or very specific approaches are much more accurate. However with higher tiers comes also increasing costs (van Leeuwen and Vermeire 2007; ECHA 2012b).

3.3 REACH guidance on occupational exposure

According to the general provision for assessing substances and preparing chemicals safety reports under REACH (see REACH Annex I and article 14), a manufacturer or importer of substances in quantities of 10 tonnes or more per year has to prepare a chemical safety assessment (CSA) of all identified uses and consider all the stages of the life-cycle of the substance. The CSA has to be based on a comparison of the potential adverse effects of a substance with the known or reasonably foreseeable exposure of man and/or the environment while taking implemented as well as recommended risk management measures and operational conditions into account. In order to assess the “foreseeable exposure of man”, ECHA has prepared a number of technical guidance documents on occupational exposure, consumer exposure and exposure to humans via the environment. Specifically, REACH guidance document R.14 provides technical guidance to manufacturers on occupational exposure estimation (ECHA 2012b). In this document, the occupational exposure assessment is measured according to different tiers. The first tier exposure estimation provides conservative (worst-case) estimates based on a limited data set. For higher tiers much more specific information and knowledge are required. In all of the REACH guidance documents, it is a general principle that measured data or appropriate analogous data have the highest importance. When these cannot be provided, modelled estimations can be used. Furthermore, the REACH guidance document on occupational exposure assessment (ECHA 2012a) defines the type of information needed and the rating criteria to be followed in occupational exposure estimations. Specifically, the duration and the frequency of exposure along with the concentration of the substance are identified as the main parameters influencing inhalation as well as dermal and oral exposure. The concentration is normally presented as an average concentration over a reference period of a full work shift of 8 hours. REACH technical guidance document R.14 also outlines a number of parameters that have to be taken into account for exposure estimations such as the characteristics of a substances and of a product, the processes, tasks and work activities in which workers are engaged, as well as work conditions and risk management measures (ECHA 2012b).

The technical guidance document R.14 also provides information and a pros and cons analysis of a number of tools that can be used for first and higher tier occupational exposure estimation. First Tier tools such as ECETOC Targeted Risk Assessment (ECETOC TRA), MEASE and the EMKG-Expo-Tool have been developed to be both easy to use and inherently conservative. According to R.14, they are best used as initial screening tools as they allow a defined range of operational conditions (OCs) and risk management measures (RMMs) to be identified and evaluated quickly. Higher tier tools such as Stoffenmanager, RISKOFDERM and the Advanced REACH tool can be used when the tier 1 assessment indicates that the level of protection is not adequate (ECHA 2012b).

In the following, a brief overview of tier 1 and higher tier exposure assessment tools as described in the ECHA guidance document R.14 will be presented.

3.3.1 Tier 1 exposure assessment tools

ECETOC TRA

ECETOC TRA uses established exposure prediction models known as EASE (Estimation and Assessment of Substance Exposure) exposure model-to-model inhalation and dermal worker exposures. EASE was originally developed by the UK Health and Safety Executive (HSE, 2003) but has since been modified by industry experts. It also considers common practices in the workplace, for example the selection of Process Categories (PROC) and Risk Management Measures (RMM). This enables a wider user community to make rapid and conservative assessments, which can be used as a first tier to demonstrate low risk for a specific scenario of use. It also removes the subsequent need to collect and use measured exposure data for another assessment of the same scenario. In using ECETOC TRA, a description of the type and basic conditions of use of substances is generated which can potentially be translated into a calculated exposure measurement using an exposure model (Liguori et al. 2016a; Paper I).

MEASE

The tool MEASE combines the EASE model with the health risk assessment guidance for metals in order to generate a first tier inhalation and dermal occupational exposure estimates of metals and inorganic substances.

When it comes to inhalation exposure, MEASE uses the same PROC approach as the ECETOC TRA tool by selecting initial exposure estimates from

three fugacity classes i.e. low, medium and high. This is defined by and based on the physical form, the melting point of the metal, the temperature of the process, the vapour pressure and the selected PROC.

For dermal exposure, MEASE is based on the system of exposure bands of the broadly used EASE system. However, the generated exposure estimates are based on measured data from several metals, collated and plotted against the EASE exposure classes. In many regards, the MEASE tool is similar to ECETOC TRA, but MEASE deviates from ECETOC TRA in some of its basic assumptions and possible default parameters. Furthermore, as it is a new tool, no validation is available yet.

EMKG-Expo-Tool

The EMKG-Expo-Tool is a generic easy-to-use workplace control scheme for hazardous substances. It was originally developed to help small and medium-sized companies derive a tier 1 inhalation exposure value for the workplace. The EMKG-Expo-Tool can be used as a generic tool for assessing and comparing the level of exposure with limit values (OEL¹, DNEL²). However, the tool is based on the banding approach of the COSHH Essentials qualitative approach to guide the assessment and management of workplace risks (HSE 1999). R.14 states that the tool should be used as an approach for filtering the non-risky workplace situations from those that require detailed attention (Liguori et al. 2016a: Paper I).

3.3.2 Higher Tier Exposure assessment tools

Stoffenmanager

Stoffenmanager was originally a web-based risk prioritizing tool for small and medium-sized enterprises. Version 4.0 includes a quantitative model for estimating inhalation exposure to vapours, aerosols of low volatility liquids and inhalable dusts.

“The web-based tool now has a specific REACH section and a section for exposure calculations in which e.g. full shift time weighted averages can be calculated. An exposure database containing around 1000 measurements with all relevant Stoffenmanager parameters is used to further underpin and vali-

¹ Occupational Exposure Limit value indicates the highest acceptable concentration of a hazardous substance in the workplace.

² The Derived No-Effect Level or DNEL is the level of exposure to the substance above which humans should not be exposed. REACH Annex I, 1.0.1 - Regulation (EC) No 1272/2008.

date the model. The database is still growing to allow future further validations and updates of the model” (ECHA 2012a).

RISKOFDERM

“The RISKOFDERM dermal model is the result of the European 5th framework programme project focused solely on dermal exposures in industrial and professional settings (Warren et al. 2006). On the basis of measured data, approaches were developed to assess dermal exposure for six different so-called Dermal Exposure Operation units (DEO units). It assesses potential dermal exposure, i.e. exposure on the skin and on the layers (of clothing or e.g. gloves) covering the skin. It therefore does not take into account any protective effect of clothing or gloves .

The basic estimate made by RISKOFDERM is the potential exposure per minute (for hands and/or remainder of the body). Total exposure over a longer period is calculated by entering the duration of the activity leading to exposure.” (ECHA 2012a).

Advanced REACH Tool (ART)

“The ART approach makes use of mechanistically modelled estimates of exposure and any relevant measurements of exposure. The tool provides estimates of the whole distribution of exposure variability and uncertainty, allowing the user to produce a variety of realistic and reasonable worst-case exposure estimates, depending on the requirements of the particular risk assessment.” (Tielemans et al. 2011; ECHA 2012b; Liguori et al. 2016a: Paper I).

The tool incorporates both a mechanistic model and an empirical part with information from an exposure database. Both parts are combined using a Bayesian statistical process in order to produce exposure estimates for specific scenarios relevant to the REACH process. ART cannot be used, however, for nanomaterials because the model has not been calibrated with data or nanomaterials exposure scenarios (ECHA 2012a; Liguori et al. 2016a: Paper I).

3.4 Exposure assessment of nanomaterials

When it comes to assessments of occupational exposure to nanomaterials, there are some complex issues that must be taken into account. Nanomaterials can have different health impacts when compared to their similar chemical in bulk form. However, considering that a nanoparticle aerosol can be described by several physical and chemical parameters, such as the size-distribution and

the shape of the particles (nano-objects as well as their aggregates and agglomerates), the particle number, the surface area or the mass concentrations, a number of different measurement methods have to be applied to get an in-depth understanding of the airborne exposure (Nel et al. 2006; Schneider 2007; Kosk-Bienko 2009; Hussein et al. 2015; Levin 2015; Levin et al. 2015b). Moreover, the important points to consider is the difficulty in airborne measurements to discriminate between nanomaterials and background particles and the difficulty in revealing if and when the aggregates/agglomerates can break back into smaller particles. Therefore, it is not possible to connect the risk directly to the particles. As illustrated in Figure 4, diverse mechanisms and different inter-particle forces can cause agglomeration in powders as well as in airborne dust. These include physical interlock (i.e. due to chain-branched or overlaps by rough particle surfaces or entangled forms of flexible fibres), soft bridging (i.e. due to adsorbed liquids or sticky surfaces or surface functionalization), and electrostatic or magnetic forces (Schneider 2007; Schneider and Jensen 2009; Hussein et al. 2015; Levin et al. 2015a: Paper IV)

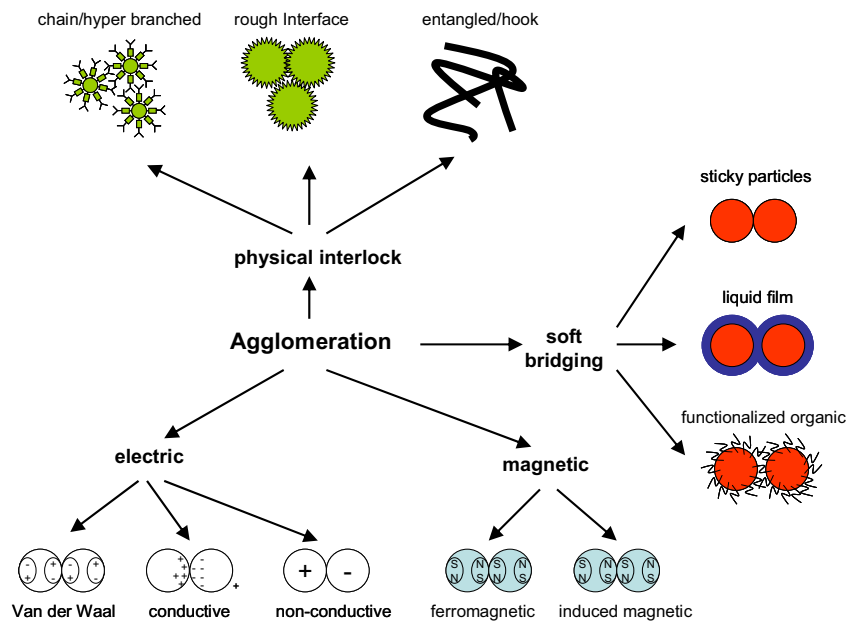


Figure 4: Schematic overview of physical properties with potential significant impact on MNP coagulation rates and inter-particle forces (Schneider and Jensen 2009).

The physical and chemical properties, for instance, change with size, diffusion becomes more important, and low level gravitational forces may become negligible, whereas electromagnetic forces may become dominant (The Royal Society 2004; Roduner 2006; Maynard and Aitken 2007; Kosk-Bienko 2009; Lead and Smith 2009).

Moreover, which metric to be measured and for which purpose is also an important matter; for instance, the size distribution will differ depending on the metric. In fact, it is different whether one chooses to measure the number, which normally is dominated by smaller particles, or the mass, which normally is determined by larger particles. This is important to acknowledge both for measurements and for modelling (Maynard and Aitken 2007; Asbach 2015; OECD 2015b)

Nanomaterial exposure assessment and management at the workplace is not as straightforward as assessment of chemical exposure to volatile chemicals. This is due to the potential mixing of the nanomaterial with background aerosols and physical transformation and size-dependent phenomena as described above (Schneider and Jensen 2009; Schneider et al. 2011a). There are also still several challenges for the development of a suitable model occupational risk assessment of nanomaterials, and there are several issues in dust measurements as currently complex specialist equipment is needed, and existing instruments often show artefacts during measurement of dusts with complex morphologies (Asbach 2015; Levin et al. 2015b)

Guidance, frameworks and decision support tools to assess the health and environmental risks of nanomaterials have been proposed in recent years. They are frequently cited and evaluated as alternative risk assessment approaches (Schneider 2007; Linkov and Satterstrom 2008; Grieger et al. 2012). These include, among others: the Nano Risk Framework, (DuPont) developed with the aim of being a practical and comprehensive framework “to evaluate and address the potential risks of nanoscale materials” (Defense 2007); the Multi-Criteria Decision Analysis (MCDA), a decision analytical framework with the aim of balancing societal benefits and unintended side effects and risks of nanomaterials (Linkov et al. 2007); the British Standard Institution Published Document pragmatic guidance on how to safely handle and dispose of manufactured nanomaterials (BSI 2007) and the NanoRiskCat, a systematic decision-support tool with the aim of helping companies and regulators with the identification of the potential risk of nanomaterials in consumer products (Hansen et al. 2014).

CB and exposure modelling are used, among other approaches, to control the potential occupational risk of nanomaterials. Exposure models for occupational inhalation exposure to nanoparticles are based on the source-transmission-receptor deterministic approach developed by Schneider et al. (2011a). The contaminant may be transported from the source through com-

partments to the receptor. However, nanoparticles may be subject to some transformation due to the physical and chemical characteristics of the aerosol. Therefore, those potential transformations have to be taken into account in the exposure model for occupational inhalation exposure to nanoparticles. This is basically a key issue that discriminates the applicability of a conventional mechanistic model from inhalation exposure model for nanomaterials. Figure 5 illustrates the conceptual mechanistic model for inhalation exposure of nanomaterials. It also shows the modelling of the physical and chemical characteristic and transformation (e.g. size distribution, deposition, coagulation) influencing the nanoparticle at the different compartments during the transportation of aerosol from the source to the receptor (Schneider et al. 2011a).

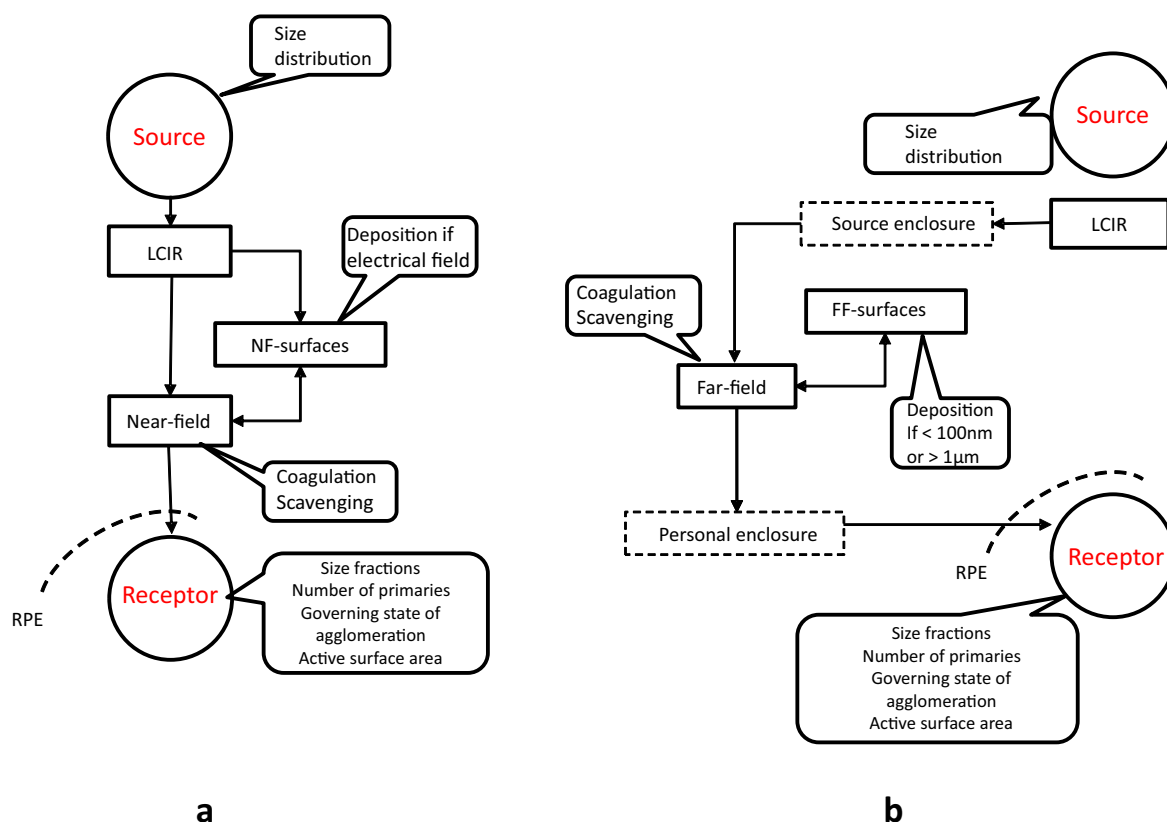


Figure 5: Illustration of the conceptual model (a) near-field (NF) source and (b) far-field (FF) source. The rectangles indicate the compartments, whereas the callouts indicate the transport processes. LCIR, local control influence region; RPE, respiratory protective devices. Adapted from Schneider et al. (2011a)

Considering, among other challenges, the absence of occupational exposure limits for the majority of nanomaterials, the not fully understood behaviour of airborne nanoparticles and the lack of appropriate exposure metrics, the

OECD Working Party on Manufactured Nanomaterials (WPMN) has suggested a harmonized tiered approach in order to assess the potential exposure to nanomaterials at workplaces (OECD 2015b). The approach consists of three-tiers: tier 1 is the first step consisting in gathering information on the workplace, tier 2 is a step where some simple measurements can be done at the workplace with easy-to-use and portable equipment; and tier 3 represents advanced measurements to be done in the workplace.

4 Control Banding tools and key parameters for exposure assessment

This chapter will introduce some of the CB tools developed for nanomaterials and identify their key parameters by comparing and analysing the tools. A full analysis of tools has been carried out and the results presented in paper I. The tools examined include the Control Banding Nanotool, IVAM Guidance, Stoffenmanager Nano 1.0, ANSES CB Tool, NanoSafer 1.0, and the Precautionary Matrix version 3.0.

4.1 Control Banding (CB)

CB is a simplified approach for assessing and managing risks associated with chemical exposure in the workplace. This is especially useful when there is a lack of knowledge such as: an absence of established occupational exposure limit values (OEL) or in case of a knowledge gap when new risks emerge from the use of chemicals (NIOSH 2009; Zalk 2010). In generic terms, CB is a qualitative approach to risk assessment and occupational risk management that groups the risk control into bands (Liguori et al. 2016a: Paper I).

In the initial conceptual basis for CB there is a four-level hierarchy of strategy control:

- 1) Good occupational hygiene practices (i.e. general ventilation, use of personal protective equipment)
- 2) Engineering controls (i.e. local exhaust ventilation)
- 3) Containment
- 4) The need to seek specialist advice

Within the initial Control Band concept, a simplified strategy called Control of Substances Hazardous to Health (COSHH) Essentials was developed in 1999 by the United Kingdom Health and Safety Executive (HSE) to assess health risks in the workplace with the COSHH regulations (NIOSH 2009; Zalk DM 2010; Liguori et al. 2016a: Paper I).

The newer CB approaches are also intended for use by non-experts, while the older models were developed for use by occupational safety, health and hygiene (OSHH) experts (Zalk DM, 2010). CB is also an invaluable risk communication tool within and between OSHH professionals (Zalk DM, 2010).

The CB strategy consists of grouping the occupational risk in bands based on combinations of hazard and exposure information. The numbers to associate with bands or risk levels are determined by balancing the complexity and difficulty of the hazard with the needs of the workers. In the CB approach the number of bands or risk levels is generally four. Theoretically, it would simplify matters for workers if there were only two risk levels: an unsafe situation (red light) and a safe situation (green light). However four bands help to avoid the ambiguity of different and potentially inappropriate judgments of the risks in between situations (possibly yellow light) essentially by dividing the yellow into two, and allowing for a more accurate choice which should then ensure appropriate control (NIOSH 2009; Zalk DM 2010; Liguori et al. 2016a: Paper I).

4.2 Control Banding based tools for nanomaterials

A number of CB-type tools have already been developed and designed primarily for the control of occupational airway exposure, which is also the current key priority in general risk management of NM (Brouwer, 2012; Liguori et al., 2016a: Paper I; Stone et al., 2014).

A summary and analysis of each of the most frequently discussed nanomaterial CB tools is given in Liguori et al. (2016a: Paper I) and the results are summarized below.

4.2.1 The Control-Banding Nanotool - CB Nanotool

The CB Nanotool was intended to enable precautionary qualitative risk assessment to protect researchers at the Lawrence Livermore National Laboratory (Paik et al. 2008; Zalk et al. 2009; Zalk and Paik 2010). It is a simplified approach for both experts and non-experts. It accounts for factors determining the extent to which employees may be potentially exposed to nanomaterials. The CB Nanotool allocates four bands for hazard (severity score), four bands for exposure (probability score) and four risk level (RL) control bands. The overall level of risk and corresponding control band is determined by a matrix arranged with the probability scores in the columns and the severity scores in the rows. The maximum probability/severity score is 100.

4.2.2 IVAM Guidance.

The IVAM Guidance (Cornelissen et al. 2011) was developed in collaboration between employers and employees to provide a guide to working safely with engineered NM and end products. The system has a list of ten generic default activities to help the user make an inventory of the potential nano-

material release during the life cycle. It allocates three bands for the hazard ranking, three bands for the exposure ranking and three control level bands. The control level bands are classified in three control levels: A is the lowest ranking, B is the middle ranking and C is the highest. There is corresponding advice on control measures for each control level.

4.2.3 Stoffenmanager Nano 1.0

Stoffenmanager Nano (Van Duuren-Stuurman et al. 2012) is a nano-specific module supporting the generic Stoffenmanager risk-banding tool used in the assessment of NM during synthesis, in powders, sprays and embedded in products. It was developed by TNO and Arbo Unie in the Netherlands. The Stoffenmanager Nano tool was developed as a practical tool for employers and employees to use in risk prioritization in exposure situations where quantitative risk assessment is currently not possible. Stoffenmanager Nano can assess the risk both excluding and including risk management measures such as local exhaust ventilation and personal protection equipment. Stoffenmanager Nano allocates five bands for hazard, four bands for exposure and three for CB. In the publication Van Duuren-Stuurman et al. (2012), the control bands are classified into three priority bands corresponding to low/medium/high priority of action. In the web-tool, the system gives the user the risk prioritization for the specific task assessed and the “risk time” taking both duration and frequency over the long-term into account.

4.2.4 ANSES CB Nanotool

The ANSES CB Nanotool was developed by the Agency for Food, Environmental and Occupational Health & Safety (ANSES) of France to be applied to conducting risk assessment and the risk management of work with manufactured nanomaterials or nano-enabled products in industrial settings (Ostiguy et al. 2010; Riediker et al. 2012a). ANSES applies five hazard bands, four exposure bands (emission potential) and five control bands for risk. The control bands (levels) consist of combinations of the hazard and exposure (emission potential) bands in a two-dimensional decision matrix, ranking from low (CL1) to high (CL5), which are accompanied by general recommendations.

4.2.5 NanoSafer

The NanoSafer tool (Kristensen et al., 2010) is a web-based combined control banding and risk management tool originally developed primarily for assisting small and medium-sized companies with limited or no experience of producing or working with nanomaterials and/or with insufficient resources to

perform a full precautionary risk assessment. The NanoSafer system has recently been updated to version (Jensen et al., 2016: Paper III) and will be briefly introduced in Chapter 5.1. In the NanoSafer model, four bands are allocated for the hazard, five bands for exposure and five risk levels (control bands). Each control band (risk level) is associated with general recommendations for risk management and action to be taken into consideration. It also contains an e-learning tool with inspiration on how to reduce exposure or risk thereof (Liguori et al. 2016a: Paper I, 2016b: Paper II; Jensen et al., 2016: Paper III).

For further explanation and details on NanoSafer see Chapter 5: a case study on the CB tool NanoSafer.

4.2.6 The Swiss Precautionary Matrix

The Swiss Precautionary Matrix is a risk categorization tool and cannot be properly categorized as a “conventional” CB-based tool. However, it has some interesting concepts that are relevant for comparison with CB tools. It was developed by the Swiss Federal Office of Public Health and Federal Office for the Environment (Höck et al. 2008, 2011; Höck, et al. 2013). It is intended to help trade and industry who produce or use nanomaterials and nano-enabled products identify possible sources of risk arising from production, use and disposal, and take workers, consumers and the environment into consideration. The outcome is a score that can be smaller or greater than 20; if the outcome is greater than 20, the Precautionary Matrix suggests a need for action (Liguori et al. 2016a; Paper I).

4.3 Determinant key parameters for exposure assessment

In an effort to identify the most important input parameters included for CB assessments and their use, a detailed analysis was made of each CB tool.

Identification of a set of key exposure parameters does not necessarily mean that they are all main parameters for the exposure evaluation since the analysis does not include a sensitivity analysis of the models .

In chapter 5 the results of such a sensitivity analysis of one of the models is described.

4.3.1 Scope and application domains and Input parameters

From the scope of each of the tools, it is noted that the CB tools were developed for different purposes and none of them was developed with consideration given to REACH requirements (Liguori et al., 2016a Paper I).

CB tools differ greatly in regard to the input parameters required and used for both hazard and exposure assessment. The number of input parameters found to be important for the exposure estimations can vary from one or three (IVAM Guidance, ANSES) to 13 (NanoSafer 1.0) and 26 (Stoffenmanager Nano 1.0), including exposure characterization and control measures (Liguori et al. 2016a: Paper I).

4.3.2 Banding allocation and scaling principle

Our analysis (Liguori et al. 2016a; Paper I) shows that the CB tools differ with regards to the number of bands that they assign to hazard, to exposure and to the risk control. The hazard and exposure bands are also allocated in different ways and consider different levels of detail. Table 1 gives an overview of the banding allocation and scaling principles in the terms of what the CB nano tools take into account for scaling them (Liguori et al. 2016a: Paper I)

Table 1: Overview of banding allocation and scaling principle of the CB nano tools. Adapted from Liguori et al. 2016a: Paper I

Name	Hazard		Exposure		Risk	
	Bands	Scaling	Bands	Scaling	Bands	Scaling
CB Nanotool	4	Sum of scores of the Nanomaterial: Surface Chemistry, Particle Shape, Particle Diameter, Solubility, CMR, Dermal Toxicity, Asthmagen weighted 70% and on the Bulk material: OEL, CMR, Toxicity, Dermal Toxicity, Asthmagen weighted 30%	4	Sum of scores of the estimated amount of material used, dustiness/mistiness, number of employees with similar exposure, frequency of operation, duration of operation.	4	Hazard and exposure scores combined in a decision matrix
ANSES CB Tool	5	Stepwise approach taking into account: if the nanomaterial is biopersistent fibre, solubility and reactivity	4	Based on the physical form of the nanomaterial and on its potential changes due to natural tendency of the material or to the process operation	5	
Stoffenmanager Nano	5	Stepwise approach taking into account: water solubility, discrimination of persistent nanofibers, nanoparticle specific hazard, classification based on insufficient toxicological data	4	Based on the source to receptor model and taking into account: duration, frequency, background concentration, concentration in the near field, concentration in the far field, control measure at worker, personal protective equipment	3	
NanoSafer	4	Taking into account: the morphology of the primary nanomaterial, chemical surface modification, the OEL for the nearest analogue bulk material, risk phrases for the nearest analogue bulk material, and water solubility	5	Based on the: emission rate or the dustiness index combined with the activity handling energy and mass handled in each work cycle; duration of work cycle; pause between work cycles; number of work cycles; amount of nanomaterial handled in each transfer; time required for each transfer; volume of the work room; and the air-change rate.	5	
IVAM Guidance	3	Water solubility Synthetic/persistent nanomaterials Fibrous non soluble nanomaterials	3	No emission Emission of embedded particles is possible Emission of free particles is possible	3	

As illustrated in Table 1, exposure banding in the CB Nanotool is based on the sum of all points allocated for each of the five parameters for exposure (named Probability score in CB Nanotool) (Liguori et al. 2016a: Paper I).

The exposure bands (called emission potential levels) in the ANSES tool are determined using a completely different approach. It allocates the potential emission according to the physical nature and location of the nanomaterial as powder, liquid or embedded in a matrix (Liguori et al. 2016a: Paper I).

The Exposure band allocation in Stoffenmanager Nano is based on the principles in the source-to-receptor model described in Schneider et al. (Schneider et al. 2011a), and evaluates different parameters (Liguori et al. 2016a: Paper I).

In NanoSafer, exposure evaluation is made based on user-defined scenarios and the principle, as in Stoffenmanager Nano, follows the conceptual model for the assessment of inhalation exposure developed by Schneider et al. (Schneider et al. 2011a). However, the final scaling of exposure considers a theoretical nano-specific exposure limit derived from the hazard assessment module and considers the volume-specific surface area of the nanomaterial (Liguori et al. 2016a: Paper I).

In the IVAM Guidance the banding allocation takes into account only whether or not emission is possible, and whether the nanomaterial in exam is embedded in a matrix or consists of a free nanoparticle (Liguori et al. 2016a: Paper I).

The Precautionary Matrix is an exception, because it cannot be considered a “conventional” CB tool. For this reason it has not been included in Table 1. However, a key parameter for estimating the potential exposure, in the Precautionary Matrix tool, is also the physical state of the material. And the scaling is further refined to take into consideration the amount of material used and the frequency with which a worker handles the nanomaterial. As previously mentioned, it is important to keep in mind that the Swiss Precautionary Matrix differs from the other tools in that it is not aimed at a band allocation but rather at determining whether there is a need for action or not (Liguori et al. 2016a: Paper I).

4.3.3 Exposure assessment parameters

As seen in Table 1, some tools (e.g. IVAM Guidance and ANSES) base the exposure assessment on a limited number of parameters, mainly focusing on the physicochemical properties and material characterization. Others like

Stoffenmanager Nano and NanoSafer base the exposure on more parameters and consequently include contextual information related to processes in the workplace and the characterization of control measures for a more elaborate assessment of work scenarios that are more in line with the S-T-R model (Figure 5) (Liguori et al. 2016a: Paper I).

Amount

The amount of NMs handled and the frequency of handling the NMs are key parameters for the CB Nanotool, the Precautionary Matrix, Stoffenmanager Nano and NanoSafer (Liguori et al. 2016a: Paper I). In the Precautionary Matrix and the CB Nanotool, the amount used refers to the amount used in one day. Stoffenmanager Nano considers the amount as the exact weight percentage in the material, intermediate, spray or end-product. In NanoSafer the exposure assessment is based on the total amount used in the process (the work cycle) as well as the amount used per task in the work cycle, coupled with information on duration, the volume of the work-room and air-change rates (Liguori et al. 2016a: Paper I).

Duration and frequency

The parameter duration of the work cycle includes the short term (15 minute) and long term (8-hour) exposure in NanoSafer. Stoffenmanager Nano estimates both the risk in the specific process and the long-term risk by taking the long-term frequency of use into account, and also the task-specific risk (Liguori et al. 2016a: Paper I).

The frequency of handling the NMs is a key parameter for the CB Nanotool, the Precautionary Matrix, Stoffenmanager Nano and NanoSafer. The Precautionary Matrix takes into account the frequency with which a worker handles the nanomaterial. In Stoffenmanager Nano and in the CB Nanotool the frequency parameter is used in the same way, for example the daily or monthly frequency of handling the NMs, while in NanoSafer the frequency parameters accounts for the number of work cycles per day. In spite of its clear importance in understanding the exposure, frequency is not considered a core information requirement for Tier 1 exposure scenarios in the ECHA Guidance R.14 on occupational exposure estimation (Liguori et al. 2016a: Paper I).

Room size and ventilation rate

When it comes to parameters related to the workplace it is noteworthy that room size and ventilation rate are only taken into account in Stoffenmanager Nano and NanoSafer (Liguori et al. 2016a: Paper I). The room size and the

ventilation rate are important parameters that control the dilution of the contaminants in the room. They are also considered a modifying factor in the S-T-R model. Room size is also a parameter considered in all Tier 1 REACH tools (Liguori et al. 2016a: Paper I).

Background and local control measures

In contrast to the other tools, Stoffenmanager Nano also considers other workplace related parameters. It allows for two input parameters for determining the background source by asking whether the machines are well maintained and whether the workplace is cleaned daily. These parameters, in combination with the intrinsic emission, are key for calculating the background concentration. Moreover, parameters accounting for the local control measures are only considered in Stoffenmanager Nano where it is used as a multiplier to calculate the potential exposure.

4.3.4 The Control Band outcome

As with many of the other CB tools reviewed here, the control band (risk levels) is a combination of the hazard and exposure bands inserted in a two-dimensional decision matrix, ranking from low to high risk level (Liguori et al. 2016a: Paper I).

Besides differing with regards to the number of bands and how the hazard and exposure bands are allocated, the CB tools also differ in the number of control bands (risk level) outcome (Liguori et al. 2016a: Paper I). Moreover there are also differences in the typology used to report the outcome; some tools associate the control-banding risk level with a general risk management recommendation on the level of engineered and personal exposure control that should be applied. Other tools associate the control-banding risk level to ranking priority of action needed (Liguori et al. 2016a: Paper I). In order to clearly identify these differences, the different control levels and associated risk communication are summarized in Table 2.

Evidently, these observed differences in both input parameters and the output format make it doubtful that it is possible to perform a quantitative comparison of their performance and immediately combine the different models into a larger holistic framework (Liguori et al. 2016a: Paper I).

Table 2: Recommended engineering control based on CB Nanotool risk level. Adapted from Liguori et al. 2016a: Paper I

Control level	Risk communication
<i>Control Banding Nanotool</i>	
RL1	General ventilation
RL2	Fume hoods or local exhaust ventilation
RL3	Containment
RL4	Seek specialist advice
<i>IVAM Guidance</i>	
A	Apply sufficient (room) ventilation, if needed local exhaust ventilation and/or containment of the emission source and use appropriate personal protective equipment.
B	According to the hierarchic Occupational Hygienic Strategy, the technical and organizational feasible protective measures are evaluated on their economical feasibility. Control measures will be based on this evaluation.
C	The hierarchic Occupational Hygienic Strategy will be strictly applied and all protective measures that are both technically and organizationally feasible will be implemented.
<i>Stoffenmanager Nano</i>	
1	High priority
2	Medium priority
3	Low priority
<i>ANSES CB tool</i>	
CL1	Natural or mechanical general ventilation
CL2	Local ventilation: extractor hood, slot hood, arm hood, table hood, and so forth
CL3	Enclosed ventilation: ventilated booth, fume hood, closed reactor with regular opening
CL4	Full containment: continuously closed systems
CL5	Full containment and review by a specialist required: seek expert advice

<i>NanoSafer</i>	
RL1	Very low toxicity and low exposure potential. The risk level is expected to be acceptable. The work may require use of local exhaust ventilation, fume hood etc. Make sure to have personal respiratory protection equipment (P3 or higher quality) available in case of accidents.
RL2	Low toxicity and/or low exposure potential. As minimum local exhaust ventilation, fume hoods etc. should be applied. The work may be performed in combination with use of respiratory protection equipment (P3 or higher quality). Make sure to have the personal respiratory protection equipment available in case of accidents.
RL3	Moderate toxicity and/or moderate exposure potential. The work should be fume-hood or with high efficient local exhaust ventilation in combination with combination with use of respiratory protection equipment (P3 or higher quality). Make sure to have the personal respiratory protection equipment available in case of accidents.
RL4	High toxicity and/or high exposure potential. Use highly efficient local exhaust ventilation, fume-hood, glove-box etc. Make sure to have the personal respiratory protection equipment (P3 or higher quality) available in case of accidents.
RL5	Very high toxicity and/or moderate to very high exposure. The work should be conducted in a fume-hood, separate enclosure etc. Air-supplied respirators or highly efficient filter masks (P3 or higher quality) may use as a supplement and must be readily available in case of accidents. Expert advice is recommended.
<i>Precautionary Matrix</i>	
A	The nanospecific need for action can be rated as low even without further clarification.
B	Nanospecific action is needed. Existing measures should be reviewed, further clarification undertaken and, if necessary, measures to reduce the risk associated with manufacturing, use and disposal implemented in the interests of precaution.

4.3.5 Application test of the CB tools

The CB tools were tested in four scenarios using a combination of two different nanomaterials (i.e. ZnO and TiO₂) and two different types of working process activities. The working process activity of scooping/filling bags in small scale production was used to test ZnO in Scenario 1 and TiO₂ in Scenario 2. The working process activity of pouring powder into a twin-screw extruder was used to test ZnO in Scenario 3 and TiO₂ in Scenario 4. The worker was considered to be located in the near-field zone in all assessments. A summary of the two activities and material information are presented in Tables 3a and 3b.

The results of the tests are collected in Table 4 and 5. Table 4 summarizes the risk band levels determined by the tools in each scenario assessed. From the result of the test it can be noted that some of the tools i.e., IVAM Guidance, ANSES and Precautionary Matrix, are more precautionary. They go very high up in the control banding immediately, and the risk level of the control recommendation is very high from the beginning, whereas other tools i.e., Stoffenmanager Nano, NanoSafer and Control Banding Nanotool, are somewhere in between lower and higher risk level and being in some extent less conservative. This can be observed comparing Scenario 1 and Scenario 3 where activities plays a role and of makes the difference between the tools. Tables 5a to 5d represent the advice or general recommendations suggested by the tools as control measures corresponding to the control level per each scenario.

Table 3a: Input parameters for two occupational exposure scenarios used in the test

	Activity 1	Activity 2
Total amount used in the operation	50 g (5 x 10g)	100kg (5 x 20 kg)
Amount per each cycle	10 g	20 kg
Activity energy factors level	0.1	0.5
Number of workers involved at work station	1	1
Duration of the operation	75 min	30 min
Frequency of the operation	daily	daily
Period between each cycle	6 min	1 min
Frequency of the cycle	1 time per day	1 time per day
Duration of each cycle	10 min	5 min
Room size	3.5 x 5 x 2.9	4 x 5 x 3.5
Ventilation rate	5 h-1	5 h-1

Table 3b: Information on the nanomaterials used in the test

Nanomaterials info		
	ZnO	TiO ₂
CAS number	1314-13-2	13463-67-7
Surface Modification (coated/fictionalized) YES/NO	NO	NO
Primary size [nm]	7.8 -- 18.6 (13.2 ±5.4)	1-10
Specific Density [g/cm ³]	5.61	4.23
S ₀ [g/L]	Insoluble	Insoluble
Specific Surface Area [m ² /g]	18 (12 – 24)	140
Respirable Dustiness Index	Moderate (259 mg/kg)	Very Low (0-10 mg/kg)
OEL [mg/m ³]	5 (4 as Zn)	10 (6 as Ti)
Hazard R-Phrases	(R50, R53)	R40

Table 4: Control band output from the four scenarios used in the test

	Scenario 1 ZnO Activity 1	Scenario 2 TiO ₂ Activity 1	Scenario 3 ZnO Activity 2	Scenario 4 TiO ₂ Activity 2
	Risk Band	Risk Band	Risk Band	Risk Band
ANSES	3 (of 5)	3 (of 5)	3 (of 5)	3 (of 5)
IVAM Guidance	3 (of 3)	3 (of 3)	3 (of 3)	3 (of 3)
Stoffenmanager Nano	1 (of 3)	2 (of 3)	1 (of 3)	3 (of 3)
NanoSafer	1 (of 5)	1 (of 5)	5 (of 5)	1 (of 5)
CB Nanotool	1 (of 4)	2 (of 4)	1 (of 4)	2 (of 4)
Precautionary Matrix	score over 20	score over 20	score over 20	score over 20

In bold is represented the control band (risk level) outcome for each scenario (columns) and for each CB nano tool (row); in parenthesis is represented the highest band for the tool. For the Precautionary Matrix tool the result is presented in terms of whether the final score is higher or lower than 20.

Table 5a: Recommendations for control measures for the different control bands

	Scenario 1: ZnO scooping 50 g	
	Control Band	Recommendations
ANSES	3 of 5	CB 3: enclosed ventilation: ventilated booth, fume hood, closed reactor with regular opening
IVAM Guidance	3 of 3	C: The hierarchic Occupational Hygienic Strategy will be strictly applied and all protective measures that are both technically and organizationally feasible will be implemented
Stoffenmanager Nano	1 of 3	III = low risk priority
Nanosafer	1 of 5	RL1: Very low toxicity and low exposure potential. The risk level is expected to be acceptable. The work may require use of local exhaust ventilation, fume hood etc. Make sure to have personal respiratory protection equipment (P3 or higher quality) available in case of accidents.
CB Nanotool	1 of 4	RL 1: General ventilation;
Precautionary Matrix	> 20	Nanospecific action is needed. Existing measures should be reviewed, further clarification undertaken and, if necessary, measures to reduce the risk associated with manufacturing, use and disposal implemented in the interest of precaution.

Table 5b: Recommendations for control measures for the different control bands

	Scenario 2: TiO₂ scooping 50 g	
	Control Band	Recommendations
ANSES	5 of 5	CB 5: full containment and review by a specialist required: seek expert advice.
IVAM Guidance	3 of 3	C: The hierarchic Occupational Hygienic Strategy will be strictly applied and all protective measures that are both technically and organizationally feasible will be implemented
Stoffenmanager Nano	2 of 3	II = medium risk priority
Nanosafer	1 of 5	RL1: Very low toxicity and low exposure potential. The risk level is expected to be acceptable. The work may require use of local exhaust ventilation, fume hood etc. Make sure to have personal respiratory protection equipment (P3 or higher quality) available in case of accidents.
CB Nanotool	2 of 4	RL 2: Fume hoods or local exhaust ventilation;
Precautionary Matrix	> 20	Nanospecific action is needed. Existing measures should be reviewed, further clarification undertaken and, if necessary, measures to reduce the risk associated with manufacturing, use and disposal implemented in the interests of precaution.

Table 5c: Recommendations for control measures for the different control bands

	Scenario 3: ZnO pouring powder 100kg	
	Control Band	Recommendations
ANSES	3 of 5	CB 3: enclosed ventilation: ventilated booth, fume hood, closed reactor with regular opening
IVAM Guidance	3 of 3	C: The hierarchic Occupational Hygienic Strategy will be strictly applied and all protective measures that are both technically and organizationally feasible will be implemented
Stoffenmanager Nano	1 of 3	III = low risk priority
Nanosafer	5 of 5	RL5: Very high toxicity and/or moderate to very high exposure. The work should be conducted in a fume-hood, separate enclosure etc. Air-supplied respirators or highly efficient filter masks (P3 or higher quality) may be used as a supplement and must be readily available in case of accidents. Expert advice is recommended.
CB Nanotool	1 of 4	RL 1: General ventilation;
Precautionary Matrix	> 20	Nanospecific action is needed. Existing measures should be reviewed, further clarification undertaken and, if necessary, measures to reduce the risk associated with manufacturing, use and disposal implemented in the interests of precaution.

Table 5d: Recommendations for control measures for the different control bands

	Scenario 4: TiO₂ pouring powder 100kg	
	Control Band	Recommendations
ANSES	5 of 5	CB 5: full containment and review by a specialist required: seek expert advice.
IVAM Guidance	3 of 3	C: The hierarchic Occupational Hygienic Strategy will be strictly applied and all protective measures that are both technically and organizationally feasible will be implemented
Stoffenmanager Nano	3 of 3	I = high risk priority
Nanosafer	1 of 5	RL1: Very low toxicity and low exposure potential. The risk level is expected to be acceptable. The work may require use of local exhaust ventilation, fume hood etc. Make sure to have personal respiratory protection equipment (P3 or higher quality) available in case of accidents.
CB Nanotool	2 of 4	RL 2: Fume hoods or local exhaust ventilation;
Precautionary Matrix	> 20	Nanospecific action is needed. Existing measures should be reviewed, further clarification undertaken and, if necessary, measures to reduce the risk associated with manufacturing, use and disposal implemented in the interests of precaution.

4.3.6 Readiness of the CB models for application in regulatory exposure assessment

The simplest tools when it comes to input requirements are the ANSES and IVAM Guidance tools, while NanoSafer and Stoffenmanager Nano are the most complex tools as they have many more mandatory input parameters (Liguori et al. 2016a: Paper I). NanoSafer and Stoffenmanager Nano also have the highest number of input parameters complying with the Source-Transmission-Receptor (STR) model (Schneider et al. 2011a) and with the ECHA Guidance R.14 input parameters (Liguori et al. 2016a: Paper I).

The applicability and scope of Stoffenmanager Nano and NanoSafer is very similar to Stoffenmanager 4.0 and the Advanced REACH Tool (ART) (Liguori et al. 2016a: Paper I). The input parameters are very similar in both number and nature when comparing the Stoffenmanager Nano and NanoSafer with the type of information needed at higher tiers for a proper occupational exposure assessment, as indicated by the ECHA technical guidance document R.14. In this respect, it seems that NanoSafer and Stoffenmanager Nano are more advanced and suitable for inclusion in R.14 (Liguori et al. 2016a: Paper I). Stoffenmanager Nano and NanoSafer, however, focus specifically on inhalation and work is needed to develop CB tools for estimating dermal and oral exposure to make the model applications more holistic (Liguori et al. 2016a: Paper I).

Overall, it seems that, among all the CB tools analysed, Stoffenmanager Nano and NanoSafer have the closest resemblance to the conceptual exposure assessment model by Schneider et al. (Schneider et al. 2011a) and the core information requirements of the ECHA Guidance R.14 (Liguori et al. 2016a: Paper I). Regarding the input parameters, Stoffenmanager Nano and NanoSafer are somewhere in between the ECHA Guidance R.14 Tier 1 and higher Tier requirements including the aerosol-dynamic modelling of the STR type (Source-Transmission-Receptor). However, the relative importance of the different additional input parameters considered in the STR model compared to simpler models is not known and should be further investigated in future work. As an example, Chapter 5 contains an in-depth analysis on a specific case in order to investigate the applicability and lessons learnt from one of these tools (Liguori et al. 2016a: Paper I).

5 A case study on the Control Banding tool NanoSafer

This chapter will present the NanoSafer 1.1 exposure assessment algorithm (Jensen et al., 2016: Paper III) and a sensitivity analysis of the core of the aerosol dispersion model. The sensitivity analysis was performed to identify input parameters to which the model output is sensitive and to test their potential variation in order considering acute and long-term occupational exposure scenarios. The discussion is based on the results in Liguori et al., (2016b: paper II).

In order to contextualize the analysis conducted here, it is important to note the premise under which the analysis was performed: in this study, NanoSafer model was subjected to sensitivity and uncertainty analysis to demonstrate the model and improve the understanding of the influence of each of the input parameters on the overall performance of the model. The analysis performed here can be defined as the second stage (*“model demonstration testing”*) in a model development sequence consisting of the five stages: 1. *model formulation and development*, 2. *demonstration testing*, 3. *Calibration*, 4. *performance testing*, 5. *Validation*.

In this chapter I first introduce the NanoSafer exposure assessment model and the approach used for the analysis. Then the sensitivity of the model input parameters will be evaluated by examining the effect on the model output as a function of the variation in the input parameters. The results from the sensitivity analysis will be used in order to determine the relative importance of the different input parameters, which could be used to identify key input parameters for further development of CB tools.

5.1 NanoSafer

The NanoSafer CB model is currently being updated to version 1.1 to also include the results from the analysis in Liguori et al. (2016b: Paper II). The modifications, among others, consist in modification of the near-field volume, improvement of the aerosol decay model and near-field-far-field air-change model, and the ability to perform assessments on nanomaterials with non-specific occupational exposure limits or other target exposure limits (Jensen et al.: Paper III). In the new version it is highlighted that the tool also addresses the primary needs for administrative workplace safety assessments and can be used by both workplace safety officers and administrative inspec-

tors to assess whether further investigation of a work process is needed (Liguori et al. 2016b: Paper II).

The final outcome of a NanoSafer control banding assessment is a combination of the estimated hazard for the specific nanomaterial used and a case-specific estimated exposure potential. There are no changes to the procedures for assessing the exposure and associated control bands as compared to version 1.0. Hence, the potential exposure level is based on an estimate of the time-resolved potential exposure levels in the near field (NF) and far field (FF), for both short term (15 min) and long term (8 hours) exposure risk, based on specific work processes. The final exposure bands consist of five levels derived from the exposure potential and the OEL for the analogue bulk material scaled against the specific surface area of the nanomaterial under evaluation.

5.1.1 NanoSafer exposure algorithm

The exposure assessment algorithm in the NanoSafer is based on a first order quantitative source to receptor exposure assessment modeling as formulated by Schneider et al. (2011), without taking into consideration aerosol deposition and coagulation (see full explanation in Jensen et al. Paper III). The dispersion model is a simple two-box model instant mixing aerosol model, which allows estimation of the time-resolved potential exposure concentrations in the near-field (around the process) and in the far-field surrounding the near-field. The time-resolved exposure assessments, enables NanoSafer to calculate and/or rank both the short term (15 minute) and the long term (8-hour) exposure risk during powder handling and emissions from fugitive/point-sources.

The estimated exposure potential is calculated as function of four elements: $f(E_i, C, W, V)$: E = Process Emission Rate; C = Process Contextual Information; W = Work-Place Dimension; V = Air Change Rate). However, the number of input parameters required for exposure assessment varies depending on the exposure scenario. The fugitive/constant emission process type requires 6 input parameters: *Duration of Work Cycle*; *Pause between Work Cycles*; *Number of Work Cycles*; *Volume of the Work Room*; *Air Change Rate*; *Constant Source Emission*; whereas for the powder handling 10 input parameters are required: the *Duration of Work Cycle*; *Pause between Work Cycles*; *Number of Work Cycles*; *Volume of the Work Room*; *Air Change Rate*; *Dustiness Index*; *Handling Energy*; *Total Amount Used per Cycle*; *Time per each Transfer*; *Amount Used per each Transfer*. The source compartment

can be considered as the most important compartment to the exposure estimate (Riedmann et al. 2015). Therefore, the analysis focuses on evaluating the parameters engaged on the fugitive/constant emission process type and on the near-field/far-field distribution of the source emission.

The exposure potential is calculated using a two-box-type near-field (NF) and far-field (FF) instant mixing model. Figure 6 shows a sketch of the working principles of the model for a full explanation see in Jensen et al. (Paper III).

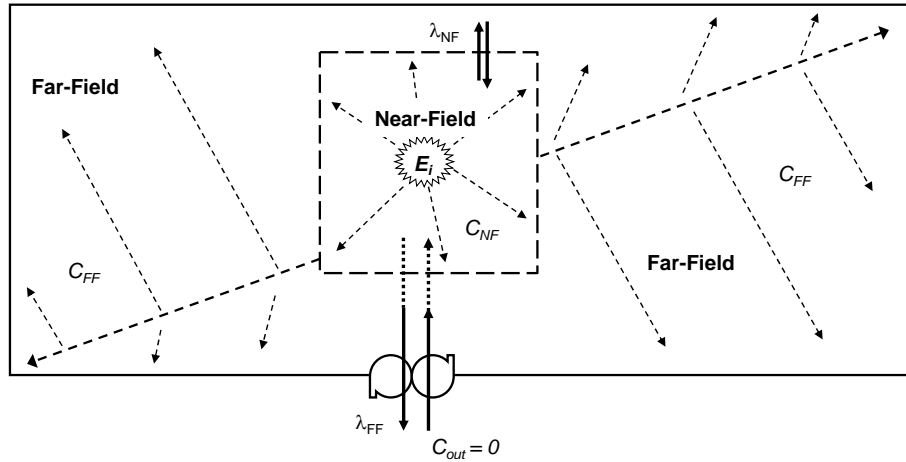


Figure 6: Sketch showing the principles in the NANOSAFER model. Arrow lines indicate air-flow and dust transport pathways. E_i : Substance emission rate; C_{NF} : Concentration near-field; C_{FF} : Concentration in far-field; λ_{FF} : air change rate in general ventilation; λ_{NF} : air change rate between the near-field and far-field volumes.

5.2 Sensitivity Analysis

In this section the analysis has been performed taking into consideration the constant emission process type. In addition, the input parameters *Duration of Work Cycle*, *Pause between Work Cycle*, *Number of Work Cycles*, *Volume of the Work Room*, *Air Change Rate*, and *Constant Source Emission* have been taken into account for the calculations of the exposure potential (Liguori et al. 2016b: Paper II).

The sensitivity analysis was performed in order to determine the degree to which an input parameter affects the model output. Different terms are used by many authors such as ‘sensitive’, ‘important’, ‘most influential’, ‘major contributor’, ‘effective’, in this work we refer to sensitivity analysis when referring to which input parameters have significant influence on model output and uncertainty analysis when referring to parameter importance (Hamby 1994). The sensitivity analysis has been conducted by applying the One-at-a-time (OAT) method and uncertainty analysis has been conducted by applying

the Factorial Design (FD) method (Box et al. 1978, 2005; Saltelli et al. 2008; Taylor 2009). Uncertainty analysis was moreover supported by graphical analysis of model output (Liguori et al. 2016b: Paper II).

Sensitivity analysis of the exposure assessment module of NanoSafer was performed to identify the factors that contribute most to the output and gain further insight into the influence of uncertainties on input parameters on the model output. Because of the NanoSafer model conditions and restrictions it was considered the deterministic approach in which the input parameters value and relative ranges of changes were predefined and there is no ability for the parameter to vary from the given values (Liguori et al. 2016b: Paper II). Therefore the sensitivity analysis was conducted by applying to a chosen set of input parameters the One-at-a-time (OAT) method (Daniel 1973; Saltelli et al. 2008; Taylor 2009). The input parameter values were chosen based on the boundary conditions of NanoSafer model and taking into account the model restriction on the authors' judgements and used as starting points for each of the parameters for the OAT sensitivity analysis. A full explanation can be seen Liguori et al., (2016b: paper II).

5.2.1 One-at-a-time test design

The One-at-a-time method was applied in order to examine the influence that the change of an input parameter has on the output exposure potential. A set of input parameter was identified as base set and then an input matrix was generated by increasing and decreasing each value of the base set by 5%, 25% and 50%, respectively (Table 6). With the exception of the *Pause between Work Cycles*; and *Number of Work Cycles* parameters where the percent variation was adjusted according to NanoSafer algorithm specifications and MATLAB restrictions. NanoSafer and MATLAB require a discrete input values for the *Duration of the Work Cycle*, the *Pause between Work Cycles* and the *Number of Work Cycles*. The value should moreover be ≥ 1 for the latter. The input matrix was then computed in MATLAB.

Table 6. Input parameter base set values and their changes for the OAT analysis.

Inputs	-50%	-25%	-5%	Base	5%	25%	50%
cse	21.35	32.03	40.57	42.70	44.84	53.38	64.05
tim*	8	11	14	15	16	19	23
bre*	3	4	5	5	5	6	8
rep*	2	2	3	3	3	4	5
totvol	45.00	67.50	85.50	90	94.50	112.50	135.00
ven	0.15	0.23	0.29	0.3	0.32	0.38	0.45

cse: Constant Source Emission; tim: Duration of Work Cycle; bre: Pause between Work Cycles; rep: Number of Work Cycles; totvol: Volume of the Work Room ; ven: Air Change Rate; *Discrete value - rounded

5.2.2 Factorial Design

The factorial design approach was used to determine the main effect of each parameter in order to determine the parameter importance (Box et al. 1978, 2005; Saltelli et al. 2008). In a factorial design analysis a given number of possible values (levels) for each parameter (factor) are chosen and ran the model for all combinations of the values (Box et al. 1978, 2005; Hamby 1994; Saltelli et al. 2008).

In the factorial design it was assumed to take two possible values (levels) “*T*”: high denoted as “+” and low denoted as “-” for each parameter (factor) denoted as “*k*”. The computational cost of this factorial design would then be $l^k = 2^6$ consisting in 64 runs. However a smaller factorial design called *fractional factorial design* (Saltelli et al. 2008), denoted $l^{k-2} = 2^{6-2}$ consisting in 16 runs was applied. A design matrix in coded form with the low values denoted as -1 and the high values denoted as +1 and extended with the outcome was applied for calculation of the main effect of the parameters and the interactions between parameters. A full explanation can be seen Liguori et al., (2016b: paper II).

5.2.3 Graphical uncertainty analysis

Graphical uncertainty analysis was performed by plotting the model output of a parameter which was varied across the whole range of its base values as determined in Table 6 against the model output of the parameter that was varied across the whole range of its base values with an error of $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$, respectively.

5.3 Key parameters for the exposure assessment in NanoSafer

First of all, it is worthwhile to define the meaning of the terms “determinant” and “sensitive” used in this section. The term “determinant” is describing the importance of a parameter and is ranked accordingly, while with the term sensitive is intended the measurement of the output change influenced by changes of the input value.

One at a time design

As illustrated in Figure 7, the result of the one-at-a-time sensitivity analysis points out similarity between near-field and far-field short term (Figure 7A-Figure 7C) exposure and between near-field and far-field long term exposure (Figure 7B-Figure 7D). Illustration of near-field results was therefore considered sufficient for the description of the sensitivity analysis of NanoSafer model.

In the short term exposure, for both near-field and far-field, minor variations were observed for the *Pause between Work Cycles* (bre) and *Air Change Rate* (ven).

In near-field short term exposure (Figure 7A) high influence was observed for changes of the input parameter *Volume of the Work Room* (totvol) to the model output. To changes of the input parameter *Volume of the Work Room* (totvol) of -5%, -25% and -50%, corresponded a changes of +5%, +32% and +94% to the model output and to changes of +5%, +25% and +50%, corresponded changes of -5%, -19% and -32% to the output. Symmetric influence to the model output was observed for changes of the input parameters *Constant Source Emission* (cse). The effect to the model output changed by $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$ corresponded to the input parameter changes of $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$ respectively. Nearly symmetric influence to the model output was observed for changes of the input parameters *Duration of the Work Cycle* (tim). To the input parameter changes of -5%, -25% and -50%, corresponded a changes of -6%, -24% and -49%, and to the input parameter changes of +5%, +25% and +50%, corresponded a changes of +6%, +22% and +42%. Also the influence of the changes of the input parameters *Number of Work Cycles* (rep) can be to some extent considered symmetric to the model output. To the input parameter changes of -5%, -25% and -50%, corresponded a changes of 0%, -27% and -56%, and to the input parameter changes of +5%, +25% and +50%, corresponded a changes of 0%, +26% and +50%.

In near-field long term exposure (Figure 7B) no variations to the model output were observed for changes of input parameter *Pause between Work Cycles* (bre).

High influence was observed for changes of the input parameter *Volume of the Work Room* (totvol) to the model output. To changes of the input parameter *Volume of the Work Room* (totvol) of -5%, -25% and -50%, corresponded a changes of +5%, +32% and +94% to the model output and to changes of +5%, +25% and +50%, corresponded changes of -5%, -19% and -32% to the output. Symmetric influence to the model output was observed for changes of the input parameters *Constant Source Emission* (cse). The effect to the model output changed by $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$ corresponded to the input parameter changes of $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$ respectively. Nearly symmetric influence to the model output was observed for changes of the input parameters *Duration of the Work Cycle* (tim). To the input parameter changes of -5%, -25% and -50%, corresponded a changes of -7%, -26% and -53%, and to the input parameter changes of +5%, +25% and +50%, corresponded a changes of +6%, +26% and +51%. The influence of the changes of the input parameters *Number of Work Cycles* (rep) can be to some extent considered symmetric to the model output. To the input parameter changes of -5%, -25% and -50%, corresponded a changes of 0%, -33% and -66%, and to the input parameter changes of +5%, +25% and +50%, corresponded a changes of 0%, +32% and +63%. Also the influence of the changes of the input parameters *Air Change Rate* (ven) can be to some extent considered symmetric to the model output. To the input parameter changes of -5%, -25% and -50%, corresponded a changes of +2%, +12% and +26%, and to the input parameter changes of +5%, +25% and +50%, corresponded a changes of -2%, -10% and -19%.

The analysis pointed out that in the near-field and far-field for short term exposure (Figure 7A and Figure 7C) the model shows major sensitivity for smaller values of the input parameter *Volume of the Work Room* (totvol). On the other hand for larger values *Volume of the Work Room* (totvol) the model shows moderate sensitivity to the change of these input parameters. Opposite is the case for the input parameters *Constant Source Emission* (cse), *Duration of the Work Cycle* (tim) and *Number of Work Cycles* (rep) where for smaller values of the input parameters the theoretical concentrations is lower and for higher values of the input parameters the theoretical concentrations is higher and in both cases the influence of the changes of these input parameters is proportional to the effect on the model output. The sensitivity of the model

can be defined proportional to the change. Different is the case for the *Air Change Rate* (ven) *Pause between Work Cycles* (bre); here the model shows negligible sensitivity.

For the near-field and far-field for long term exposure (Figure 7B and Figure 7D) the analysis pointed out in contrast to the short term exposure a sensitivity of the model on the changes of the input parameter *Air Change Rate* (ven) whereas similar sensitivity of the model to the short term exposure was observed for all the other input parameters. For smaller values of *Air Change Rate* (ven) changes on the input parameter shows higher sensitivity of the model compared to the sensitivity showed for changes on the input of higher values.

The sensitivity ranking (SR) can be calculated as residual sum squared of the output obtained with base input parameter values (v) and the perturbed input parameter values as expressed by the equation 1:

$$\text{Equation 1) } SR = \sum_i (v_i^{perturbed} - v_i^{base})^2$$

Table 7 shows the results for the model sensitivity ranking of input parameters.

Table 7: Input parameter ordered according to the model sensitivity effect

	Sensitivity analysis	
Ranking	Near field short term exposure	Near-field long term exposure Far-field short and long term
1	totvol	totvol
2	rep	rep
3	cse	tim
4	tim	cse
5	ven	ven
6	bre	bre

cse: *Constant Source Emission*; tim: *Duration of Work Cycle*; bre: *Pause between Work Cycles*; rep: *Number of Work Cycles*; totvol: *Volume of the Work Room* ; ven: *Air Change Rate*;

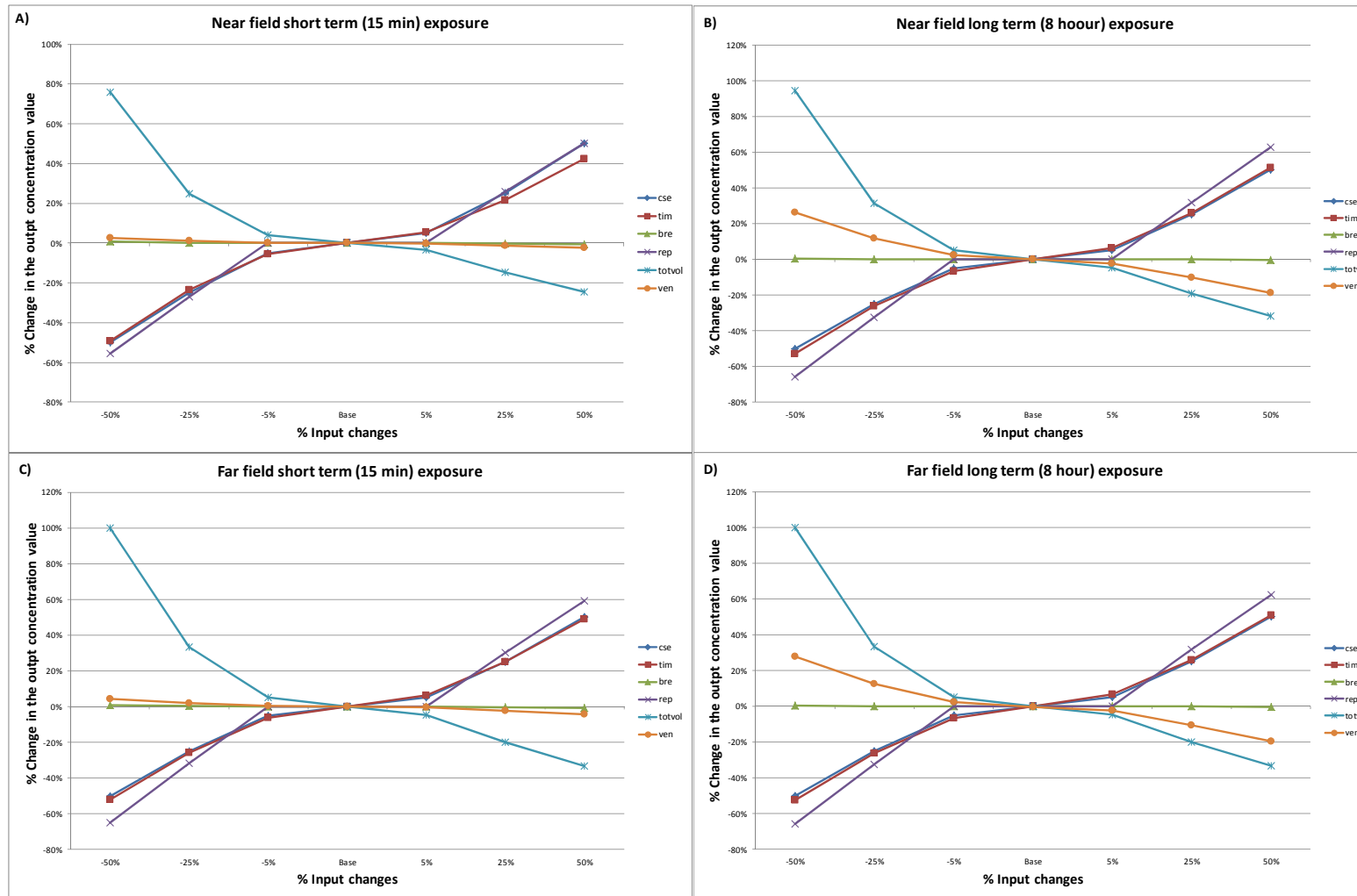


Figure 7: Influence of changes (OAT) of the input parameters (Liguori et al. 2016b: Paper II) cse: *Constant Source Emission*; tim: *Duration of Work Cycle*; bre: *Pause between Work Cycles*; rep: *Number of Work Cycles*; totvol: *Volume of the Work Room* ; ven: *Air Change Rate*;

Factorial Design

The interpretation of sensitivity analysis results will largely depend on the level of confidence or uncertainty on the input parameters (Box et al. 1978, 2005; Saltelli et al. 2008; Taylor 2009). The Factorial Design (FD) method was therefore applied in order to determine the important parameters for the model by identifying the main effect of each parameter and their interaction.

The results of the factorial design were the same for all four concentrations (Concentration in the near field and far field for long term (8 hours) and short term (15 min) exposure) and are collected in Table 8.

Table 8: Ranking of the main effect of each parameter and their interactions

	Main effects	Interactions		
1	cse	cse×tim	bre×tovol	
2	tim	cse×rep	tovol×ven	
3	rep	tim×rep	bre×ven	
4	bre	cse×bre	tim×tovol	
5	tovol	cse×tovol	tim×bre	rep×ven
6	ven	tim×ven	bre×rep	
7		cse×ven	rep×tovol	

cse: *Constant Source Emission*; tim: *Duration of Work Cycle*; bre: *Pause between Work Cycles*; rep: *Number of Work Cycles*; tovol: *Volume of the Work Room* ; ven: *Air Change Rate*;

The result points out that when fugitive emission process type is under consideration the *Constant Source Emission* is ranked as most important parameter and *Volume of the Work Room* and *Air Change Rate* are ranked as less important. On the other hand when considering the interaction between the *Volume of the Work Room* and *Pause between Work Cycles* and the interaction between *Volume of the Work Room* and *Air Change Rate*, ranked as the highest and the second highest, it makes the *Volume of the Work Room* important parameter. Similarly for the *Air Change Rate* ranked as lowest in the main effect and as second and third highest when taking into account their interaction with *Volume of the Work Room* and *Pause between Work Cycles*, respectively.

The effect of the interaction showed in Table 8 evidently arises from a difference in sensitivity to the *Volume of the Work Room* and *Air change rate*. As indicated also in Box et al. (1978): “the main effect of a parameter should be individually interpreted only if there is no evidence that the parameter interacts with other parameters”.

Graphical uncertainty analysis

Graphical uncertainty analysis was performed by plotting the model output of a parameter which was varied across the whole range of its base values as determined in Table 6 against the model output of the parameter that was varied across the whole range of its base values with a simulated imprecision of $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$, respectively.

The results pointed out that influence of the imprecision in the input parameters is higher from small values of the *Volume of the Work Room* input parameter (Figure 8), of the *Air Change Rate* input parameter (Figure 9) and of the *Duration of the Work Cycle* (Figure 10) input. Whereas a negligible influence of imprecision was observed for the *Number of Work Cycles* input parameter (Figure 11) and for the *Pause between Work Cycles* (Figure 12) up to c.a. 30 min but upper. It should be noticed that the oscillation effect observed in Figure 10, Figure 11 is less evident in Figure 12. This is caused by restriction of NanoSafer algorithm that accepts only discrete values. Therefore the value has to be rounded after the percent error changes.

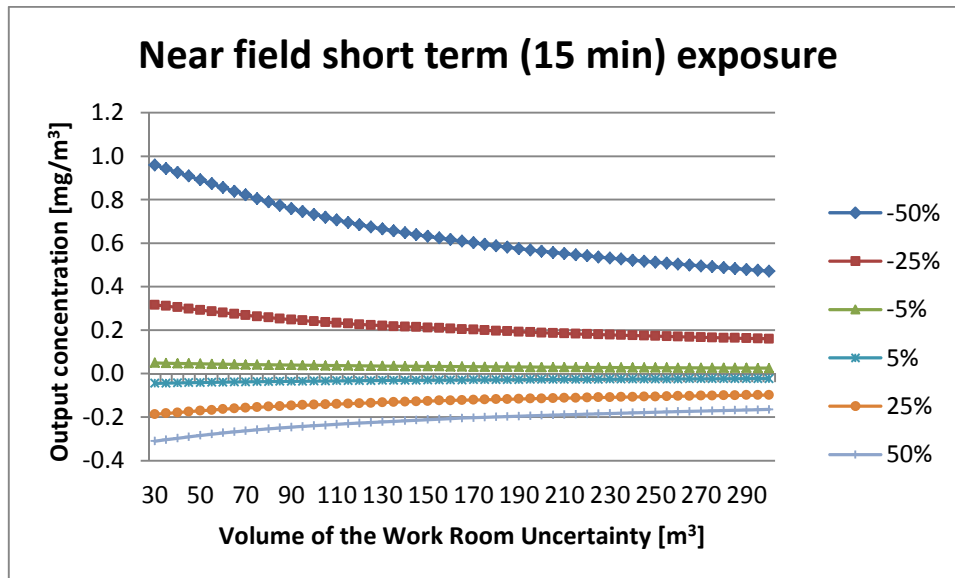


Figure 8: Model output for different *Volume of the Work Room* input values with a simulated error of $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$

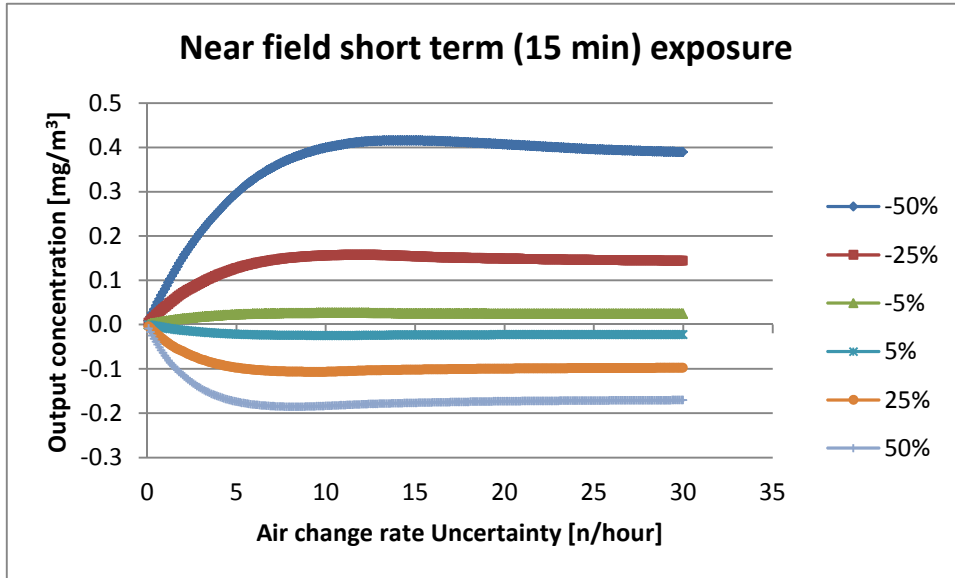


Figure 9: Model output for different *Air Change Rate* input values with a simulated error of $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$

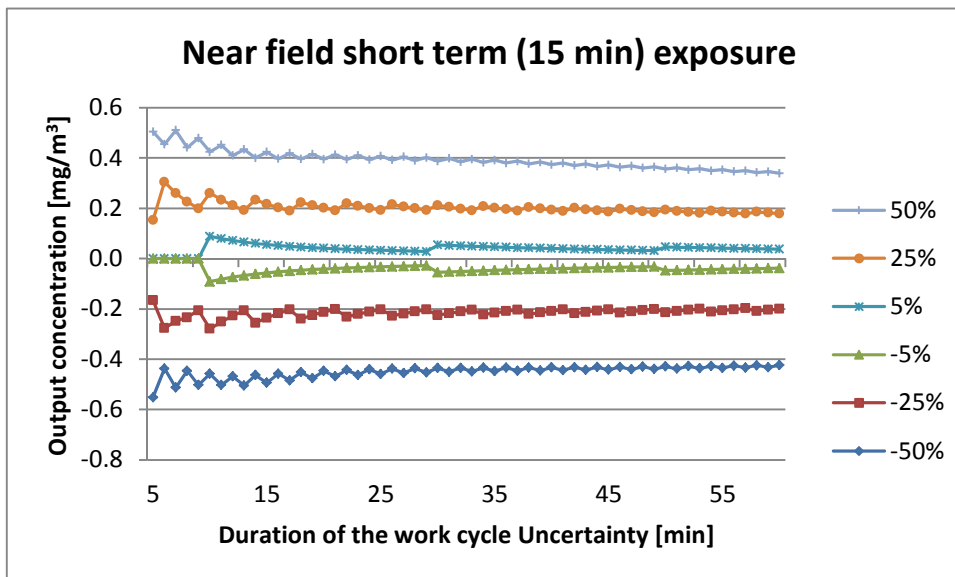


Figure 10: Model output for different *Duration of the Work Cycle* input values with a simulated error of $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$

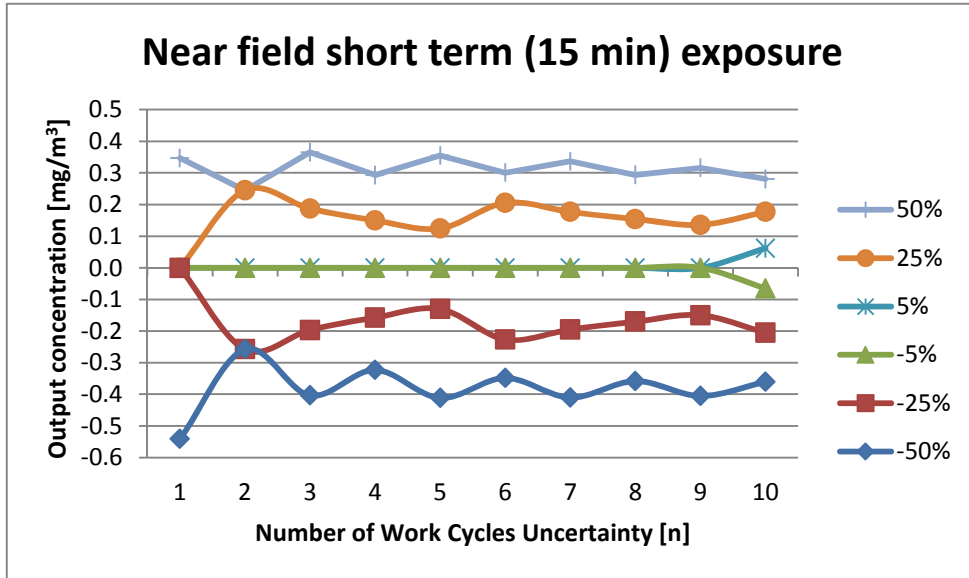


Figure 11: Model output for different *Number of Work Cycles* input values with a simulated error of $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$

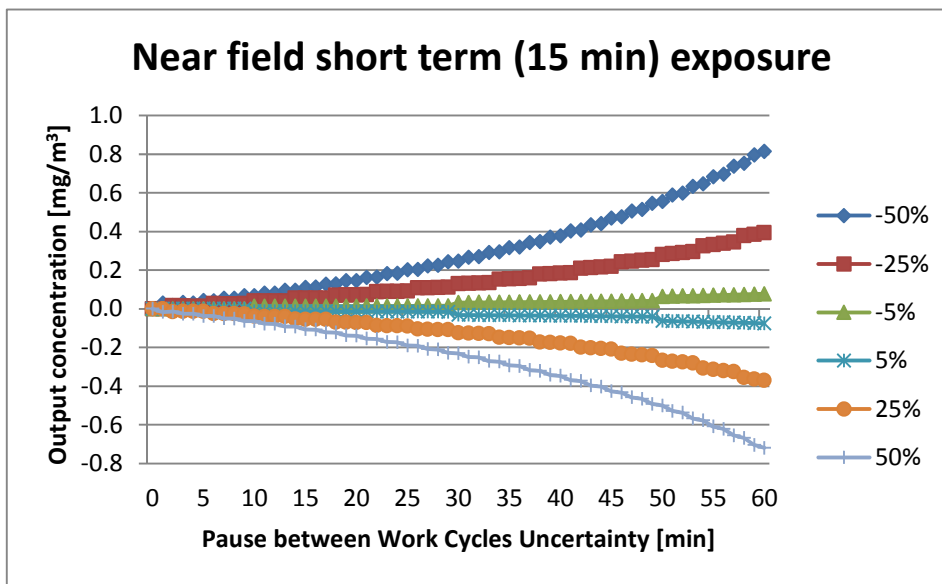


Figure 12: Model output for different *Pause between Work Cycles* input values with a simulated error of $\pm 5\%$, $\pm 25\%$ and $\pm 50\%$

Given the conditions and work scenario chosen, the analysis clearly suggests the importance of taking into account these parameters in the exposure assessment process (Liguori et al. 2016b: Paper II). However, further investigations with a different set of input parameters and different work scenarios applied also to other CB nano-tools could be beneficial to demonstrate further this conclusion.

6 Discussion and Perspectives

The aim of this PhD thesis was to evaluate existing models on the occupational exposure assessment of nanomaterials and assess them in order to identify a set of primary parameters to be applied in a CB model for a precautionary occupational exposure assessment.

Identified limitations of existing methods and approach

To date, due to crucial scientific unknowns of occupational exposure, occupational exposure limits (OEL) for nanomaterials cannot be easily established. There is, therefore, lack of OELs for various nanomaterials. As discussed in Section 3.4, nanomaterials behave significantly different than bulk materials. For example, for conventional materials it is normally considered sufficient to assess the occupational exposure using one metric alone (i.e. the mass concentration of the substance). This is different for nanomaterials. For the exposure assessment of nanomaterials, different factors (e.g. size-number distribution, mass, surface, reactivity, morphology) should most likely be taken into consideration and it will not be possible to reduce the particle exposure to a single number but rather to a combination of these metrics (e.g. a vector). It is evident then that occupational exposure assessment of nanomaterials is more complicated than for bulk size materials. (Buzea et al. 2007; Schneider 2007; Kosk-Bienko 2009; Lead and Smith 2009; Schneider and Jensen 2009; Hussein et al. 2015; Levin et al. 2015a: Paper IV).

This complexity was also acknowledged by the ECHA who provided, among others, the technical guidance appendix document R.14-4 (ECHA 2012a) and the implementations RIPoN-2 and RIPoN-3 regarding nanomaterials (Aitken et al. 2011; Hankin et al. 2011) to the industry in order to give some help with the chemical assessment for fulfilling the REACH obligations. However, one key issue of using exposure assessment tools suggested by the ECHA technical guidance document R.14 is that they assume the presence of OELs, which are available for the majority of chemicals but not for nanomaterials. The determination of an OEL for nanomaterials is challenging as there are discussions on which universal metric should be used for the assessment of the toxicity of nanomaterials (Oberdürster 2000; Donaldson et al. 2001; Warheit 2008; Kosk-Bienko 2009). The models suggested in the ECHA technical guidance are in fact based on conceptual mechanistic model for inhalation exposure assessment of conventional chemicals and, as discussed in Section 3.1, they are not applicable to nanomaterials (Liguori et al. 2016a: Paper I).

This has called for the need of development of new models targeting occupational exposure assessment of nanomaterials.

As discussed in Section 3.4, these new models have taken into account some of the major challenges related to the occupational exposure assessment of nanomaterials such as the physical and chemical properties of nanoparticles (e.g.: size-number distribution, mass, surface, reactivity, morphology), the nanoparticles behaviour (e.g., agglomeration/aggregation). It is important to take into account also the discrimination of the background as well as the instruments, measurements, and methods (Qi et al. 2009; Fissan et al. 2012; Levin 2015; OECD 2015b)

Control Banding tool as an alternative method

The development of models is progressing in parallel with the knowledge, with improvement of measurement techniques and instruments. However it is evident that there is a need for simplified and easy-to-use tools, as a group of experts worldwide also called for harmonization approach (Riediker et al. 2012b; Hunt et al. 2013). This is moreover in line with the OECD Working Party on Manufactured Nanomaterials (WPMN), in which it is pointed out, in its latest document OECD (2015b), the need of controlling the potential exposure to nanomaterials at the workplace and has therefore proposed “harmonized tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces” (OECD 2015b).

In this context CB tools can be an alternative valid approach, which can be implemented as a preliminary risk assessment at the workplace to protect workers engaged with nanomaterials. As it is a simplified approach for experts and non-experts, it accounts for factors determining the extent to which employees may be potentially exposed to nanomaterials (Zalk 2010; Liguori et al. 2016a: Paper I).

The analysis of the CB tools, conducted in Section 3.3 and 4.3, showed that for some of the tools proposed by the ECHA technical guidance document R.14 (ETEM 2014) validation is in process, while tools targeting occupational exposure assessments of nanomaterials are still under development and testing (Liguori et al. 2016a: Paper I). This could be good timing for a call of harmonization of CB tools for occupational exposure assessment of nanomaterials. As a matter of fact, the applicability of the Control Banding Nanotool, the Precautionary Matrix, the NanoSafer and Stoffenmanager

Nano, among other CB tools, has also been suggested by the OECD document for the Tier 1: Information gathering (OECD 2015b).

The tools were developed for different aims, complexities, and application domains. They have been made for different uses and consequently, the exposure assessments and derived risk levels are based on different concepts and assumptions.

Assessment of Control Banding tools used on occupational exposure to nanomaterials

Chapter 4 pointed out that the CB tools approach appears particularly interesting in the context of lack of reliable data to assess potential exposures and risks related to the production and application of nanomaterials. However, it was noted, that when it comes to comparison with REACH requirements and compliance with the Source-Transmission-Receptor (STR) model (Schneider et al. 2011b), a number of key aspects need be taken into consideration (Liguori et al. 2016a: Paper I, 2016b: Paper II).

First of all, it should be taken into account that the aim of a CB-tool in general is not to be a quantitative model, which is the aim of the STR model. The majority of CB tools were in fact developed in order to help researchers, producers and users of nanomaterials to complete first precautionary risk estimations and apply precautionary exposure control. Some were developed more with the aim to enable precautionary screening assessments to determine whether there is a need for a subsequent assessment in depth. Others were developed with the aim to protect researchers in work at laboratory scale, or to provide guidance for the organization of safe work with nanomaterials or with the aim to perform simple precautionary risk assessments without taking the contextual information at the workplace into account. Although varying greatly in focus and scope, most of the tools give guidance on how to make this first-hand assessment of the hazards and exposure associated with nanomaterials and their use(s), respectively (Liguori et al. 2016a: Paper I).

Second, several of the CB tools require a substantial number of input parameters. Some of the CB tools even ask for input parameters that are not standard information in technical and safety data sheets and not even readily available in the scientific literature (e.g. surface reactivity and degree of agglomeration). In more recent developments, test guidance to obtain this data is emerging (Höck, et al. 2013; Studer, C. et al. 2013; Liguori et al. 2016a: Paper I).

Third, most of the CB tools focus on inhalation risk only and use an estimate of the likelihood of exposure or a more-or-less precise relative scale. In CB tools, built-in hazard assessments or scaling models are necessary to enable an overall risk assessment, when the hazard is not known (Liguori et al. 2016a: Paper I).

Overall, it seems that, among all the CB tools analysed, Stoffenmanager Nano and NanoSafer have the closest resemblance with the STR conceptual exposure assessment model developed by Schneider et al. (2011) and the core information requirements of the ECHA Guidance R.14 (Liguori et al. 2016a: Paper I).

The analysis of the CB tools showed furthermore that Stoffenmanager Nano and NanoSafer use more input parameters for complying with the STR model than any of the other CB tools. This makes these tools certainly eligible for Tier 1 Information gathering as already proposed in the OECD document (OECD 2015b).

Moreover, based on the analysis of the CB tools a set of key parameters was identified. These are suggested to be taken into account for a model formulation in the development of a CB tools for preliminary risk assessment of inhalation exposure to nanomaterials. In Box 1 an overview of these is given and divided into three groups according to their relevance for the characterization of the material, workplace process and inclusion for the evaluation.

Box 1: Overview of recommended set of parameters to be included in models for occupational inhalation exposure assessment of nanomaterials.

Material and safety parameters	Workplace process related parameters	Evaluation parameters
Nanomaterial name	Activity description-Source domain	Short term (15-min) exposure
Surface Modification (coated/fictionalized) YES/NO	Activity energy factors level	Long term (8 hour) exposure
Primary size [nm]	Total amount used in the work cycle	Near-field exposure
Specific Density [g/cm ³]	Duration of each cycle	Far-field exposure
Solubility - So [g/L]	Period between each cycle	Time (duration and frequency) exposure
Specific Surface Area [m ² /g]	Frequency of the cycle	Task exposure
Respirable Dustiness Index OEL [mg/m ³]	Amount per each task in the work cycle	
Hazard R-Phrases	Time per each task in the work cycle	
Product name	Room size	
Product appearance	Ventilation rate	
Moisture content	Location of the worker during the task (near field (breathing zone)/far field)	
Concentration of the nano component	Distance employee head – product	
Containing fibres/fibre like particles	Working place maintenance and cleaning	
	Local control and PPE	

7 Conclusions

In this thesis occupational exposure assessment nanomaterials was explored. Different control banding tools and their applicability to occupational exposure assessment of nanomaterials were analysed with respect to their use range and applicability to risk assessment of nanomaterials and assist the further development of tools for exposure assessment of nanomaterials at the workplace.

As reported in the literature, workplace exposure assessment for nanomaterials is more complicated than the assessment for traditional chemicals. This is due to the physical and chemical properties and behaviour of nanomaterials in air e.g., background discrimination, aggregation and agglomeration, size and particle distribution, specific surface area, surface reactivity. All of these issues pose challenges to the measurements and the modelling applied to the assessment of nanomaterials at workplaces.

However, promising models for occupational exposure assessment of nanomaterials are under development. The OECD has recently proposed a tiered approach for workplace measurement and assessment. New conceptual models including consideration on the physical and chemical properties and behaviour of nanomaterials have been proposed. In addition, as it is illustrated in this thesis, several control banding tools for estimating the exposure to nanomaterials have been developed. Two of these tools have implemented mechanistic conceptual exposure assessment models developed for nanomaterials.

The analysis showed that:

- All tools are meant to allow for qualitative or semi-quantitative exposure assessment of nanomaterials.
- The control band (risk level) is a combination of the hazard and exposure bands in a two-dimensional decision matrix, ranking from low to high risk level.
- The existing control banding tools differ in:
 - Input parameters and output formats
 - Number of exposure and hazard bands
 - Allocation and scaling of the hazard and exposure bands
 - Number of control bands (risk level) outcome
 - Typology used to report the outcome.

These observed differences make it doubtful that it is possible to perform a direct quantitative comparison of the performance of the control banding tools and immediately combines them into a larger holistic framework. As pointed out throughout this thesis, control banding tools are suitable approaches for initial exposure assessment. However, it should be noted that the precautionary efficacy of the tools has not been truly demonstrated by industrial case studies yet.

This thesis highlights that two of the tools evaluated, NanoSafer and Stoffenmanager Nano, are more advanced, and that they are suitable for a relatively advanced exposure assessment.

The analysis of the CB tools pinpointed a set of input parameters to be taken into account.

Control banding tools represents suitable simplified and strategic components for precautionary risk management and prioritization. Moreover, control banding tools may be useful for facilitating risk communication between stakeholders involved in risk assessment at the workplace and even in communication and decisions made at the administrative and regulatory level. It is important, however, that the tools are demonstrated and tested against real data to demonstrate their protective capacity under different conditions. Moreover harmonization of a set of parameters and output formats should be encouraged in order to pursue the development of an advanced CB tool for the assessment of occupational exposure to nanomaterials.

8 References

- Aitken R, Bassan A, Friedrichs S, Hankin S, Hansen S, Holmqvist J, et al. Specific advice on exposure assessment and hazard/risk characterisation for nanomaterials under REACH (RIP-oN 3). Final Proj Report-REACH-NANO Consult-ON3FPR1FINAL. 2011;(Journal Article).
- Asbach C. Chapter 3.3 - Exposure Measurement at Workplaces A2 - Dolez, Patricia I. In: Nanoengineering [Internet]. Amsterdam: Elsevier; 2015 [cited 2016 Jan 25]. p. 523–55. Available from: <http://www.sciencedirect.com/science/article/pii/B9780444627476000166>
- ASTM. ASTM Standard E2456 (06): 2012 - Standard terminology relating to nanotechnology,". 2012.
- Box G EP, Hunter WG, Hunter JS. Statistics for experimenters: an introduction to design, data analysis, and model building. Wiley New York; 1978.
- Box GE, Hunter JS, Hunter WG. Statistics for experimenters: design, innovation, and discovery. Vol. 2. Wiley-Interscience New York; 2005.
- Brouwer DH. Control Banding Approaches for Nanomaterials. Ann Occup Hyg. 2012 Jul;56(5):506–14.
- BSI P. PD 6699-2:2007 Nanotechnologies-Part 2: Guide to safe handling and disposal of manufactured nanomaterials. BSI Lond. 2007;
- Buzea C, Pacheco II, Robbie K. Nanomaterials and nanoparticles: sources and toxicity. Biointerphases. 2007;2(4):MR17-MR71.
- Cornelissen R, Jongeneelen F, Van Broekhuizen F, Van Broekhuizen F. Guidance working safely with nanomaterials and products, the guide for employers and employees. Amst Neth. 2011;(Journal Article).
- Daniel C. One-at-a-Time Plans. J Am Stat Assoc. 1973 Jun 1;68(342):353–60.
- Defense E.- Environmental Defense & DuPont. Nano Risk Framework. Environmental Defense – DuPont Nano Partnership. 2007. Available from: <http://business.edf.org/projects/featured/past-projects/dupont-safer-nanotech/>;
- Donaldson K, Stone V, Clouter A, Renwick L, MacNee W. Ultrafine particles. Occup Environ Med. 2001;58(3):211–6.

- EC. COMMISSION REGULATION (EC) No 1488/94 of 28 June 1994 laying down the principles for the assessment of risks to man and the environment of existing substances in accordance with Council Regulation (EEC) No793/93. 1994.
- EC. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). 2006.
- EC. Commission Recommendation of 18 October 2011 on the definition of nanomaterial. 2011.
- ECHA. Guidance on information requirements and chemical safety assessment Appendix R14-4 Recommendations for nanomaterials applicable to Chapter R.14 Occupational exposure estimation. European Chemicals Agency; 2012a.
- ECHA. Guidance on information requirements and chemical safety assessment Chapter R.14: Occupational exposure estimation. European Chemicals Agency; 2012b.
- ETEAM. ETEAM Conference: The Evaluation of Tier 1 Exposure Assessment Models under Reach ('eteam') project. In Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA); 2014.
- Fissan H, Asbach C, Kaminski H, Kuhlbusch TA. Total surface area concentration measurements of nanoparticles in gases with an electrical sensor. *Chem Ing Tech*. 2012;84(3):365–72.
- Grieger KD, Linkov I, Hansen SF, Baun A. Environmental risk analysis for nanomaterials: review and evaluation of frameworks. *Nanotoxicology*. 2012;6(2):196–212.
- Hamby DM. A review of techniques for parameter sensitivity analysis of environmental models. *Environ Monit Assess*. 1994;32(2):135–54.
- Hankin S, Peters S, Poland C, Foss Hansen S, Holmqvist J, Ross B, et al. Specific advice on fulfilling information requirements for nanomaterials under REACH (RIP-oN 2). Final Proj Rep RNCRIP-ON2FPR1FINAL Eur Comm Jt Res Cent Ispra Italy. 2011;(Journal Article).
- Hansen SF, Jensen KA, Baun A. NanoRiskCat: a conceptual tool for categorization and communication of exposure potentials and hazards of nanomaterials in consumer products. *J Nanoparticle Res*. 2014;16(1):1–25.

- Herber RF, Duffus JH, Christensen JM, Olsen E, Park MV. Risk assessment for occupational exposure to chemicals. A review of current methodology (IUPAC Technical Report). Pure Appl Chem. 2001;73(6):993–1031.
- Höck, J, Epprecht, T, Furrer E, Gautschi M, Hofmann H, Höhener K, et al. Guidelines on the Precautionary Matrix for Synthetic Nanomaterials [Internet]. Federal Office of Public Health and Federal Office for the Environment; 2013. Available from: [http://www.temas.ch/WWWTEMAS/temas_homepage.nsf/vwRes/NanoSR26/\\$FILE/Wegleitung_e.pdf](http://www.temas.ch/WWWTEMAS/temas_homepage.nsf/vwRes/NanoSR26/$FILE/Wegleitung_e.pdf)
- Höck J, Epprecht T, Hofmann H, Höhener K, Krug H, Lorenz C, et al. Guidelines on the precautionary matrix for synthetic nanomaterials [Internet]. 2011. Available from: [http://www.temas.ch/wwwtemas/temas_homepage.nsf/vwRes/NanoSR26/\\$FILE/Wegleitung_e.pdf](http://www.temas.ch/wwwtemas/temas_homepage.nsf/vwRes/NanoSR26/$FILE/Wegleitung_e.pdf)
- Höck J, Hofmann H, Krug H, Lorenz C, Limbach L, Nowack B, et al. Guidelines on the precautionary matrix for synthetic nanomaterials [Internet]. 2008. Available from: [http://www.temas.ch/WWWTEMAS/temas_homepage.nsf/vwRes/Spiegel_053/\\$FILE/Guidelines+on+the+Precautionary+Matrix+for+Synthetic+Nanomaterials+June+09.pdf](http://www.temas.ch/WWWTEMAS/temas_homepage.nsf/vwRes/Spiegel_053/$FILE/Guidelines+on+the+Precautionary+Matrix+for+Synthetic+Nanomaterials+June+09.pdf)
- HSE. COSHH Essentials, Health and Safety Executive. London, UK; 1999.
- Hunt G, Lynch I, Cassee F, Handy RD, Fernandes TF, Berges M, et al. Towards a Consensus View on Understanding Nanomaterials Hazards and Managing Exposure: Knowledge Gaps and Recommendations. Materials. 2013;6(3):1090–117.
- Hussein T, Wierzbicka A, Löndahl J, Lazaridis M, Hänninen O. Indoor aerosol modeling for assessment of exposure and respiratory tract deposited dose. Atmos Environ. 2015;106:402–11.
- Hutchins B.L., Harrison A. A History of Factory Legislation. Reprinted from 1903 edition. London, UK: FRANK CASS & CO LTD; 1966.
- ILO. The Prevention Occupational Diseases [Internet]. Geneva: International Labour Organization 2013; 2013. Available from: http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---safework/documents/publication/wcms_208226.pdf
- ILO. Safety and Health at Work: A Vision for Sustainable Prevention [Internet]. International Labour Organization 2014; 2014. Available from:

http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---safework/documents/publication/wcms_301214.pdf

ILO W. Thirteenth Session of the Joint ILO/WHO Committee on Occupational Health [Internet]. Joint ILO/WHO; 2003. Available from: http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---safework/documents/publication/wcms_110478.pdf

INAIL. WHITE BOOK EXPOSURE TO ENGINEERED NANOMATERIALS AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS [Internet]. Milano: INAIL; 2011. Available from: http://www.nanotec.it/public/wp-content/uploads/2014/04/INAIL_NANOSH_network_WhiteBookNanomaterials.pdf

ISO. ISO/TR 12885: 2008 -Nanotechnologies -- Health and safety practices in occupational settings relevant to nanotechnologies [Internet]. 2008a. Available from: http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=52093

ISO. ISO/TS 27687: 2008 Nanotechnologies -- Terminology and definitions for nano-objects -- Nanoparticle, nanofibre and nanoplate [Internet]. 2008b. Available from: http://www.iso.org/iso/catalogue_detail?csnumber=44278

Jensen KA, Saber AT, Kristensen HV, Liguori B, Jensen ACØ, Koponen IK, et al. NanoSafer version 1.1: A web-based precautionary risk assessment and management tool for manufactured nanomaterials using first order modeling.

Kosk-Bienko J. Workplace exposure to nanoparticles [Internet]. Spain: EU-OSHA – European Agency for Safety and Health at Work; 2009 Mar. Report No.: 2. Available from: https://osha.europa.eu/en/tools-and-publications/publications/literature_reviews/workplace_exposure_to_nanoparticles/view

Kristensen HV, Hansen SV, Holm GR. Nanopartikler i arbejdsmiljøet: Viden og inspiration om håndtering af nanomaterialer [Internet]. 2010. Available from: http://nanosafer.ibar.dk/media/Nanopartikler_i_arbejdsmiljoet_samlet.pdf

Lead RJ, Smith E. Environmental and Human Health Impacts of Nanotechnology. WILEY; 2009.

- van Leeuwen CJ, Vermeire TG. Risk assessment of chemicals: an introduction. Springer Science & Business Media; 2007.
- Levin M. Influence of instruments performance and material properties on exposure assessment of airborne engineered nanomaterials. DTU Nanotech - PhD Thesis [Internet]. 2015; Available from: http://orbit.dtu.dk/files/116619383/Thesis_mlev_v2.pdf
- Levin M, Rojas E, Vanhala E, Vippola M, Liguori B, Kling KI, et al. Influence of relative humidity and physical load during storage on dustiness of inorganic nanomaterials: implications for testing and risk assessment. *J Nanoparticle Res.* 2015a;17(8):1–13.
- Levin M, Witschger O, Bau S, Jankowska E, Koponen IK, Koivisto AJ, et al. Can We Trust Real Time Measurements of Lung Deposited Surface Area Concentrations in Dust from Powder Nanomaterials? *Aerosol Air Qual Res.* 2015b;.
- Liguori B, Hansen SF, Baun A, Jensen KA. Control Banding Tools for Occupational Exposure Assessment of Nanomaterials – Ready for Use in a Regulatory Context? *NanoImpact* - Submitt. 2016a in press;
- Liguori B, Jensen ACØ, Hansen SF, Baun A, Jensen KA. Sensitivity Analysis of NanoSafer Control Banding Web-Tool Version 1.1: Ranking of Determining Parameters and Uncertainty. 2016b;.
- Linkov I, Satterstrom FK. Nanomaterial risk assessment and risk management. In: *Real-Time and Deliberative Decision Making*. Springer; 2008. p. 129–57.
- Linkov I, Satterstrom FK, Steevens J, Ferguson E, Pleus RC. Multi-criteria decision analysis and environmental risk assessment for nanomaterials. *J Nanoparticle Res.* 2007;9(4):543–54.
- Maynard AD. Nanotechnology: The Next Big Thing, or Much Ado about Nothing? *Ann Occup Hyg.* 2007 Jan 1;51(1):1–12.
- Maynard AD, Aitken RJ. Assessing exposure to airborne nanomaterials: current abilities and future requirements. *Nanotoxicology.* 2007;1(1):26–41.
- Nel A, Xia T, Mädler L, Li N. Toxic Potential of Materials at the Nanolevel. *Science.* 2006 Feb 3;311(5761):622–7.
- NIOSH. Qualitative Risk Characterization and Management of Occupational Hazards: Control Banding (CB) A Literature Review and Critical Analysis [Internet]. DHHS (NIOSH) Publication No. 2009–152; 2009

Aug. Available from: <http://www.cdc.gov/niosh/docs/2009-152/pdfs/2009-152.pdf>

Oberdörster G. Toxicokinetics and effects of fibrous and nonfibrous particles. *Inhal Toxicol.* 2002;14(1):29–56.

Oberdörster G. Toxicology of ultrafine particles: in vivo studies. *Philos Trans R Soc Lond Math Phys Eng Sci.* 2000;358(1775):2719–40.

OECD. ANALYSIS OF THE SURVEY ON AVAILABLE METHODS AND MODELS FOR ASSESSING EXPOSURE TO MANUFACTURED NANOMATERIALS [Internet]. OECD Environment, Health and Safety Publications; 2015a. (Series on the Safety of Manufactured Nanomaterials; vol. ENV/JM/MONO(2015)20). Available from: <http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO%282015%2920&docLanguage=En>

OECD. HARMONIZED TIERED APPROACH TO MEASURE AND ASSESS THE POTENTIAL EXPOSURE TO AIRBORNE EMISSIONS OF ENGINEERED NANO-OBJECTS AND THEIR AGGLOMERATES AND AGGREGATES AT WORKPLACES [Internet]. OECD Environment, Health and Safety Publications; 2015b. (Series on the Safety of Manufactured Nanomaterials; vol. ENV/JM/MONO(2015)19). Available from: <http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO%282015%2920&docLanguage=En>

Ostiguy C, Riediker M, Triolet J, Troisfontaines P, Vernez D. Development of a specific control banding tool for nanomaterials. *Expert Comm CES Phys Agents French Agency Food Environ Occup Health Saf Maisons-Alfort Cedex.* 2010;(Journal Article).

Paik SY, Zalk DM, Swuste P. Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. *Ann Occup Hyg.* 2008;52(6):419–28.

Qi C, Asbach C, Shin WG, Fissan H, Pui DY. The effect of particle pre-existing charge on unipolar charging and its implication on electrical aerosol measurements. *Aerosol Sci Technol.* 2009;43(3):232–40.

Richard P. Feynman. Plenty of Room at the Bottom [Internet]. 1959 [cited 2015 Oct 15]. Available from: <http://www.its.caltech.edu/~feynman/plenty.html>

- Riediker M, Ostiguy C, Triolet J, Troisfontaine P, Vernez D, Bourdel G, et al. Development of a control banding tool for nanomaterials. *J Nanomater.* 2012a;2012(Journal Article):8.
- Riediker M, Schubauer-Berigan MK, Brouwer DH, Nelissen I, Koppen G, Frijns E, et al. A road map toward a globally harmonized approach for occupational health surveillance and epidemiology in nanomaterial workers. *J Occup Environ Med Am Coll Occup Environ Med.* 2012b Oct;54(10):1214–23.
- RNCOS. Nanotechnology Market Outlook 2020 [Internet]. 2015 Apr. (RNCOS E-Services Private Limited). Available from: <http://www.researchandmarkets.com/research/kv6mm5/nanotechnology>
- Roduner E. Size matters: why nanomaterials are different. *Chem Soc Rev.* 2006 Jul;35(7):583–92.
- Saltelli A, Chan K, Scott EM. Sensitivity Analysis [Internet]. WILEY; 2008 [cited 2015 Aug 17]. Available from: <http://eu.wiley.com/WileyCDA/WileyTitle/productCd-0470743824.html>
- Schneider T. Evaluation and control of occupational health risks from nanoparticles. Nordic Council of Ministers; 2007.
- Schneider T, Brouwer DH, Koponen IK, Jensen KA, Fransman W, Van Duuren-Stuurman B, et al. Conceptual model for assessment of inhalation exposure to manufactured nanoparticles. *J Expo Sci Environ Epidemiol.* 2011a;21(5):450–63.
- Schneider T, Brouwer DH, Koponen IK, Jensen KA, Fransman W, Van Duuren-Stuurman B, et al. Conceptual model for assessment of inhalation exposure to manufactured nanoparticles. *J Expo Sci Environ Epidemiol.* 2011b Oct;21(5):450–63.
- Schneider T, Jensen KA. Relevance of aerosol dynamics and dustiness for personal exposure to manufactured nanoparticles. *J Nanoparticle Res.* 2009 Jul 28;11(7):1637–50.
- Schulte P, Geraci C, Zumwalde R, Hoover M, Kuempel E. Occupational Risk Management of Engineered Nanoparticles. *J Occup Environ Hyg.* 2008 Apr 9;5(4):239–49.

- Schulte PA GC Hodson LL, Zumwalde RD, Kuempel ED, Murashov V, Martinez KF, Heidel DS. Overview of Risk Management for Engineered Nanomaterials. *J Phys Conf Ser.* 2013;429(1):012062–012062.
- Stone V, Pozzi-Mucelli S, Tran L, Aschberger K, Sabella S, Vogel U, et al. ITS-NANO - Prioritising nanosafety research to develop a stakeholder driven intelligent testing strategy. Part Fibre Toxicol. 2014;11(Journal Article):9–11.
- Studer, C., Furrer, E., Höck, J. Leaflet on the Precautionary Matrix for Synthetic [Internet]. Federal Office of Public Health FOPH Federal Office for the Environment FOEN; 2013. Available from: [http://www.temas.ch/wwwtemas/temas_homepage.nsf/vwRes/NanoSR27/\\$FILE/Infoblatt_EN.pdf](http://www.temas.ch/wwwtemas/temas_homepage.nsf/vwRes/NanoSR27/$FILE/Infoblatt_EN.pdf)
- Taylor M. What is sensitivity analysis [Internet]. Hayward Medical Communications; 2009. Available from: <http://www.whatisseries.co.uk/wp-content/uploads/2014/07/What-is-sensitivity-analysis.png>
- The Royal Society. Nanoscience and nanotechnologies: opportunities and uncertainties [Internet]. London: The Royal Society 2004; 2004. (Science Policy Section). Available from: <http://www.nanotec.org.uk/report/Nano%20report%202004%20fin.pdf>
- Tielemans E, Schneider T, Goede H, Tischer M, Warren N, Kromhout H, et al. Conceptual model for assessment of inhalation exposure: defining modifying factors. *Ann Occup Hyg.* 2008 Oct;52(7):577–86.
- Tielemans E, Warren N, Fransman W, Van Tongeren M, McNally K, Tischer M, et al. Advanced REACH Tool (ART): overview of version 1.0 and research needs. *Ann Occup Hyg.* 2011;55(9):949–56.
- Van Duuren-Stuurman B, Vink SR, Verbist KJ, Heussen HG, Brouwer DH, Kroese DE, et al. Stoffenmanager Nano version 1.0: a web-based tool for risk prioritization of airborne manufactured nano objects. *Ann Occup Hyg.* 2012;56(5):525–41.
- Warheit DB. How meaningful are the results of nanotoxicity studies in the absence of adequate material characterization? *Toxicol Sci.* 2008;101(2):183–5.
- Warren ND, Marquart H, Christopher Y, Laitinen J, Van Hemmen JJ. Task-based dermal exposure models for regulatory risk assessment. *Ann Occup Hyg.* 2006;50(5):491–503.

- Zalk DM. CONTROL BANDING - A Simplified, Qualitative Strategy for the Assessment of Occupational Risks and Selection of solutions. United States of America: D. M. Zalk; 2010.
- Zalk DM, Paik SY. Control Banding and Nanotechnology. Synergist. 2010 Mar 10;03/10:age.
- Zalk DM, Paik SY, Swuste P. Evaluating the control banding nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. J Nanoparticle Res. 2009;11(7):1685–704.

